

The economic burden of MRSA in hospitals of the South-Eastern Norway Regional Health Authority

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Foreword

This thesis constitutes the master thesis for the degree of Master of Philosophy (M. Phil.) in “Health economics, policy and management” at the University of Oslo. It was undertaken at the Norwegian Institute of Public Health during the period November 2014-May 2015, as part of a project aimed at estimating the costs of antibiotics resistance in Norway. Resistance to antibiotics has become a serious worldwide problem as the number of pathogens that develop resistance to drugs is continuously increasing, and the development and production of new drugs is not keeping up with this increase. Methicillin-resistant *Staphylococcus aureus* (MRSA) is the most common resistant bacterium in European countries. Norway is a low-prevalence country. A report based on 1,473 *Staphylococcus aureus* isolates from Norway indicates that less than 1% of these isolates are resistant to methicillin (MRSA) (European Centre for Disease Prevention and Control, 2013), but the arduous work to keep this under control is continuous and requires much effort from health authorities and personnel. The costs of these infections have been estimated through similar cost analyses in other European countries, i.e. the Swiss study conducted by Macedo-Viñas et al. (2013) in which they estimated the mean additional costs of MRSA infections based on excess length of stay to be €7,623, and the German study by Hübner et al. (2014) in which they estimate the mean additional costs of MRSA infections to be €8,625.

The data from the Norwegian Surveillance System for Communicable Diseases and the Norwegian Patient Registry used in this cost analysis were provided by the Norwegian Institute of Public Health. The first data set we began to work with had a row of data for each patient based on every ward where they received care for one episode of inpatient care. This data set included the Diagnosis Related Group (DRG) code for each ward, rather than the hospital DRG code (refer to Figure 8). The hospital DRG code is the basis for reimbursement per episode of care. This created some difficulties in analysis, as we tried to capture our variables of interest for one episode of inpatient care. We requested a new data set from the Norwegian Patient Registry, which was received on April 1, 2015, that captured, in one row, the patient’s activity based on one episode of inpatient care. This was the data set used for our final analysis. The Norwegian Institute of Public Health had also received ethical approval from the Regional Committees for Medical and Health Research Ethics (REC) for this project. We are very grateful for the opportunity provided by the Norwegian Institute of Public Health and for the assistance we received from Petter Elstrøm, Birgitte F. DeBlasio, Oliver Kacelnik, and Jørgen V. Bjørnholt. Our academic supervisor was Ivar Sønbo Kristiansen.

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Abbreviations

CA-MRSA	Community Associated-Methicillin-resistant <i>Staphylococcus aureus</i>
CHF	Swiss Franc
CI	Confidence Interval
DRG	Diagnosis Related Groups
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
EU	European Union
€	Euro
GDP	Gross Domestic Product
HA-MRSA	Healthcare Associated- Methicillin-resistant <i>Staphylococcus aureus</i>
ICD-10	International Classification of Diseases
ICU	Intensive Care Unit
LOS	Length of Stay
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
MSIS	Norwegian Surveillance System for Communicable Diseases
MSSA	Methicillin-susceptible <i>Staphylococcus aureus</i>
NOK	Norwegian Kroner
NPR	Norwegian Patient Registry
SEK	Swedish Kroner
\$	United States Dollar
WHO	World Health Organization

Abstract

Background: Patients with Methicillin-resistant *Staphylococcus aureus* (MRSA) are thought to produce additional costs for hospitals, mainly driven by their length of stay and the costs associated with keeping the patients isolated.

Objective: The aim of our study was to assess the costs of MRSA diagnosed patients based on their length of stay, number of episodes of care, and DRG reimbursement, as well as to map out the characteristics of this patient group.

Methods: Our analyses were based on data from the year 2012 for the South-Eastern Norway Regional Health Authority as reported and registered in the Norwegian Surveillance System for Communicable Diseases and the Norwegian Patient Registry. We estimated excess length of stay by: (i) matching MRSA diagnosed inpatients with non-MRSA inpatients according to DRG code; (ii) matching MRSA diagnosed inpatients with non-MRSA inpatients based on hospital ward. We estimated the economic burden by: (i) matching MRSA diagnosed inpatients with non-MRSA inpatients based on primary diagnosis and then found the mean DRG reimbursement per group; (ii) matching MRSA diagnosed inpatients with non-MRSA inpatients based on hospital ward and compared the mean DRG reimbursement; (iii) matching MRSA diagnosed outpatients and day patients with non-MRSA patients based on ward and compared the mean DRG reimbursement. We estimated episodes of care by: (i) matching all MRSA diagnosed patients with non-MRSA patients based on hospital ward; (ii) matching MRSA diagnosed outpatients and day patients to non-MRSA patients based on ward to compare the number of subsequent episodes of hospital care per group.

Results: The mean length of stay for MRSA inpatients (n=174) was 8.5 and 8.2 days compared with controls, who had a mean length of stay of 5.4 and 4.6 days when matched on DRG code and ward, respectively. The DRG reimbursement for MRSA inpatients was NOK71,206 and NOK74,644 compared with NOK56,653 and NOK49,511 for controls matched based on primary diagnosis and ward, respectively. MRSA inpatients had nearly double (1.5) the number of subsequent episodes per patient compared with controls (0.8) matched on ward. All MRSA patients (n=315), outpatients (n=241), and day patients (n=20), had fewer subsequent episodes of care compared with their controls.

Conclusion: This analysis indicates the economic impact of patients with MRSA diagnoses, having 26%-50% higher costs than others. Further detailed cost-effectiveness analysis is advised so that policy makers can make informed decisions regarding infection control measures.

1. Introduction (both authors)

Staphylococcus aureus is classified as a gram-positive aerobic organism that is considered to be one the most frequently diagnosed bacterium in this category (Levinson, 2008). The bacterium is associated with several types of infections, most commonly skin and soft tissue infections, although it may also cause more severe infections of the bone and bloodstream (World Health Organization, 2014). Certain strains of *Staphylococcus aureus* can mediate toxin production that may lead to toxic shock syndrome, scalded skin syndrome, and food poisoning (Levinson, 2008), and it is also a leading cause of bacterial infections responsible for a number of diseases and life-threatening conditions, such as septicemia, pneumonia and endocarditis (Christenson, Ardung and Sylvan, 2011).

1.2 Methicillin-resistant *Staphylococcus aureus* (MRSA) (both authors)

Methicillin, the first anti-resistance antibiotic, was introduced in 1959 as a response to the bacterium's resistance to penicillin. Within three years of the introduction of methicillin, Methicillin-resistant *Staphylococcus aureus* (MRSA) (Figure 1) appeared (Davies and Davies, 2010). MRSA has since become a frequent cause of nosocomial infections and is associated with increased mortality and morbidity (Hübner et al., 2014). Patients who undergo organ transplantations, hemodialysis, as well as some cancer treatments are particularly susceptible to multidrug-resistant bacterial infections when receiving treatment for underlying diseases (European Centre for Disease Prevention and Control, 2009).

A meta-analysis of 30 studies by Cosgrove et al., (2003) found that the average mortality rate of septicemia was ~36% for MRSA compared to ~24% for methicillin-susceptible *Staphylococcus aureus* (MSSA). The Epic II study, an international study including data from 1,265 participating Intensive Care Units (ICU) from 75 countries, assessed the increased risk of death of MRSA infected patients in ICU compared to patients who were infected with MSSA while in ICU. Their results showed that MRSA was associated with an increased risk of hospital death of almost 50% compared to MSSA (Hanberger et al., 2011).

In the joint technical report, "The bacterial challenge; time to react", by the European Centre for Disease Prevention and Control (ECDC) and the European Medicines Agency (EMA), it is shown that MRSA is the most common multidrug-

resistant bacterium, among those under surveillance in the European Union (EU) (ECDC, 2009). The World Health Organization (WHO) estimates in its report from 2014, “The evolving threat of antimicrobial resistance”, that people with MRSA are 64% more likely to die than people with a non-resistant form of the infection. They also increase the cost of health care through lengthier hospital stays, estimated at 2,5 million extra hospital days, and extra in-hospital costs of more than €900 million in 2007 (ECDC, 2009).

At least 2 million people acquire serious infections with resistant bacteria each year in the United States, and it is estimated that at least 23,000 die as a direct consequence of these antibiotic-resistant bacteria (U.S. Department of Health and Human Services, 2013). This same report estimates that 80,461 invasive MRSA infections and 11,285 related deaths occurred in the United States in 2011. The prevalence of *Staphylococcus aureus* isolates that are resistant to methicillin (MRSA) is high in the rest of the world, from an average between 22%-25% in the EU (ECDC, 2009) to an average of 80%-90% in some health care settings in the Americas and Africa (WHO, 2014).

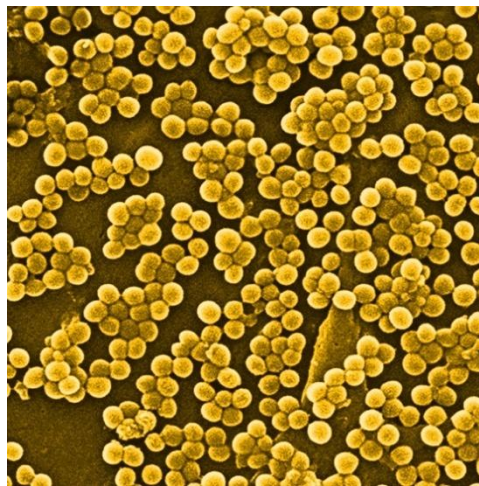


Figure 1: *Staphylococcus aureus*

(Motility research, 2015)

Staphylococcus aureus occur in clusters that resemble grapes (Staphylo)

1.2.1 Epidemiology (A.E.S.A.)

Staphylococcus aureus is a normal inhabitant in the human body, found permanently in the nose of 20%-30% of adults and sometimes on the skin (Levinson, 2008). It spreads from person to person by direct contact and through contaminated objects, rarely, but also possibly, through inhalation of contaminated droplets (Levinson, 2008).

Methicillin-resistant strains of *Staphylococcus aureus* (MRSA) are frequently categorized as either hospital- or healthcare-associated (HA-MRSA) and community-associated (CA-MRSA) infections (Enright, 2006). HA and CA-MRSA are genetically different, and therefore, CA-MRSA may be susceptible to other antibiotics than HA-MRSA, although the same drugs used to treat HA-MRSA may be effective against CA-MRSA (Levinson, 2008). There is an important distinction between MRSA colonization and infection. Patients who are deemed colonized have the bacteria present in their body, whereas, patients with active infections present with clinical symptoms (Levinson, 2008). The origins of both HA and CA-MRSA are rooted in improper use of this type of medication (Figure 2).

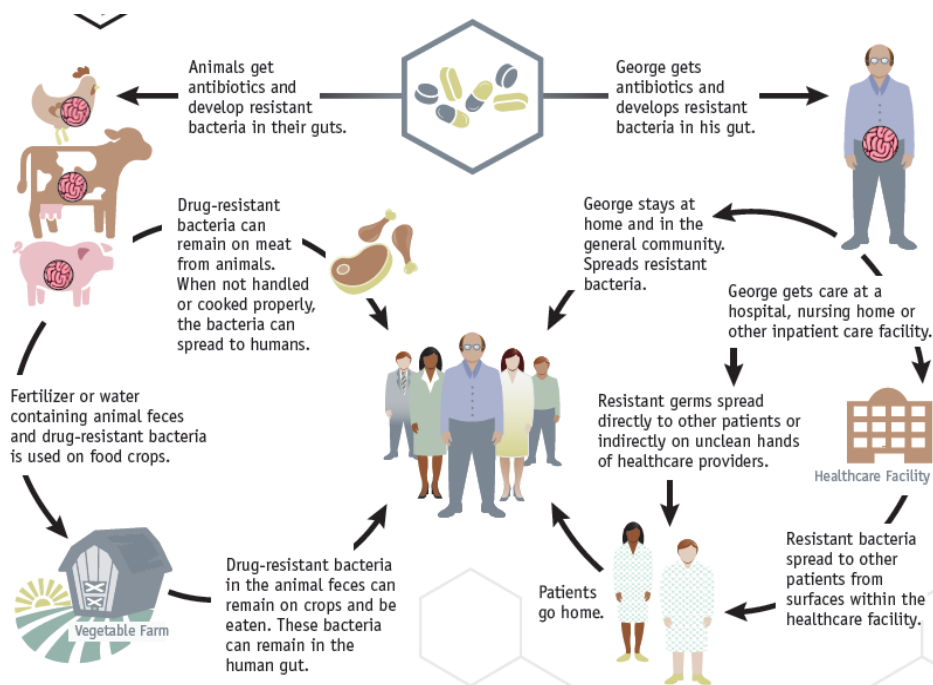


Figure 2: Examples of how antibiotic resistance spreads

(U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2013, p. 14)

1.2.2 The nature of antibiotics and bacterial resistance mechanisms (A.E.S.A.)

Before we explore how resistance mechanisms work, we must understand how antibiotics and antimicrobials in general act when administered to a patient. These drugs have the ability to act against selected bacterial or microbial functions without disadvantaging the host. Antimicrobial agents can be roughly classified into two main categories: bacteriostatic and bactericidal (Sosa et al., 2009). Bacteriostatic antibiotics and antimicrobial agents inhibit the growth and multiplication of the bacteria so the patient's immune system gets time to fight them and get rid of them, while bactericidal antimicrobial agents kill the bacteria regardless of the patient's immunity (Sosa et al., 2009).

Some bacteria are naturally resistant to certain antibiotics because they do not have target sites for the medication or because they naturally have low permeability to the agents in the medication due to differences in the chemical composition of the medication and the microbial membrane (Sosa et al., 2009). According to the Norwegian Institute of Public Health, bacteria may develop resistance to antibiotics in two main ways:

- Mutations in the genetic material (DNA) after exposure to antibiotics in the environment
- Transfer of resistance genes from other bacteria

Resistance mechanisms are developed depending on the specific pathways that the drug is intended to act on (Figure 3).

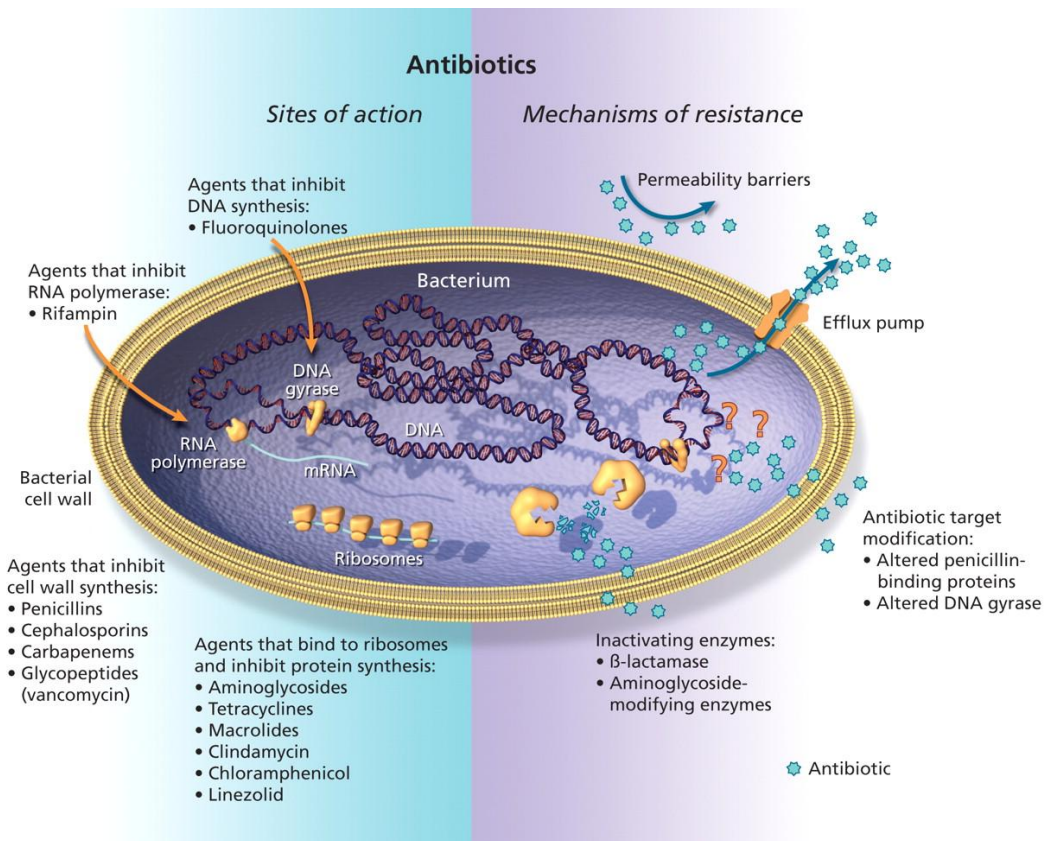


Figure 3: Sites of action and potential mechanisms of bacterial resistance to antimicrobial agents

(Canadian Medical Association (CMAJ), 2015)

Some important events in the development of antibiotic resistance include the discovery of Penicillin-resistant *Staphylococcus aureus* in 1940, the introduction of methicillin in 1960 and the development of resistance to the same by *Staphylococcus aureus* in 1962 (Figure 4). Bacteria have adapted and developed resistance to any drug intended to work against them. The main challenge with this is that, currently, there are no new drugs being developed for these purposes due to lack of return on investment for large pharmaceutical companies (Piddock, 2011).

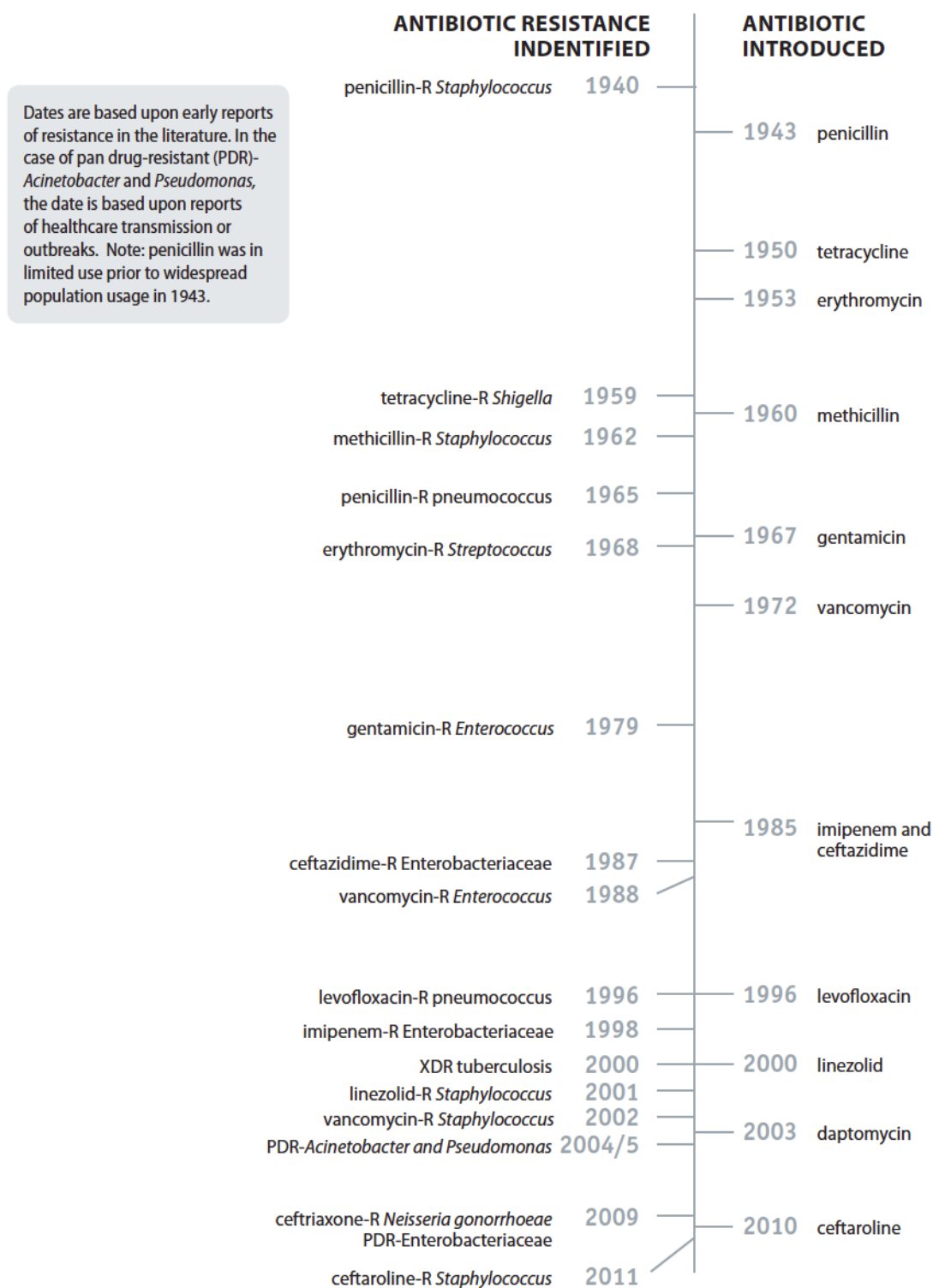


Figure 4: Timeline showing key events in antibiotic resistance from 1940 to 2011

(U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2013,p. 28)

1.3 Norway

1.3.1 Health care organization (C.I)

The Norwegian health care system is structured on three levels: national, regional, and local. The Ministry of Health and Care Services is the national branch that provides oversight, allocates the health care budget, and writes legislation for the provision of health care, among other responsibilities (Johnsen, 2006). Johnsen states that, “the Ministry of Health and Care Services is responsible for administering the following services: primary health care, specialized health care, public health, mental health, medical rehabilitation, dental services, pharmacies and pharmaceuticals, emergency planning and coordination, policies on molecular biology and biotechnology and nutrition and food safety” (Johnsen, 2006, p. 16).

The provision of specialist health care is the primary responsibility of the regional health authorities. According to the South-Eastern Norway Regional Health Authority’s website (2015), specialist care includes hospitals, psychiatric and substance abuse treatment institutions, ambulance service, emergency service response, patient transportation, rehabilitation institutions, hospital pharmacies, and laboratories. The regional level of the health care system is divided into four geographic regional health authorities: North, Central, West, and South-East. Below in Figure 5 is a depiction of these four regions.

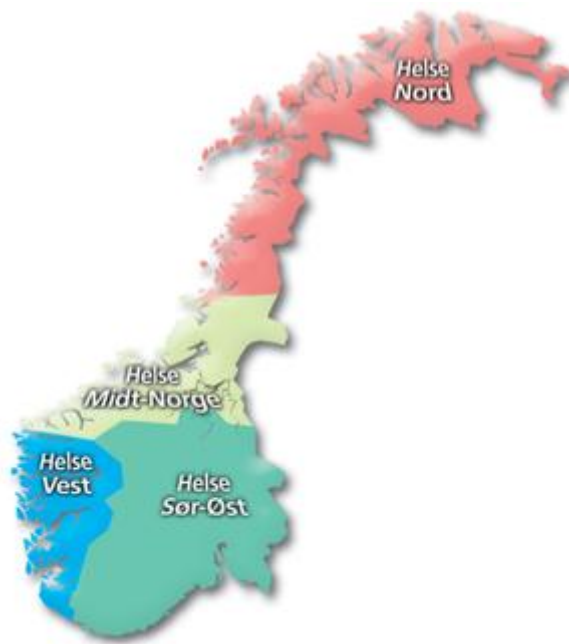


Figure 5: Map of Norway’s Regional Health Authorities

(Norwegian Government, 2015)

The Regional Health Authorities are responsible for providing specialist care services through their hospital trusts (also known as hospital enterprises) and individual hospitals within their region (Figure 6).

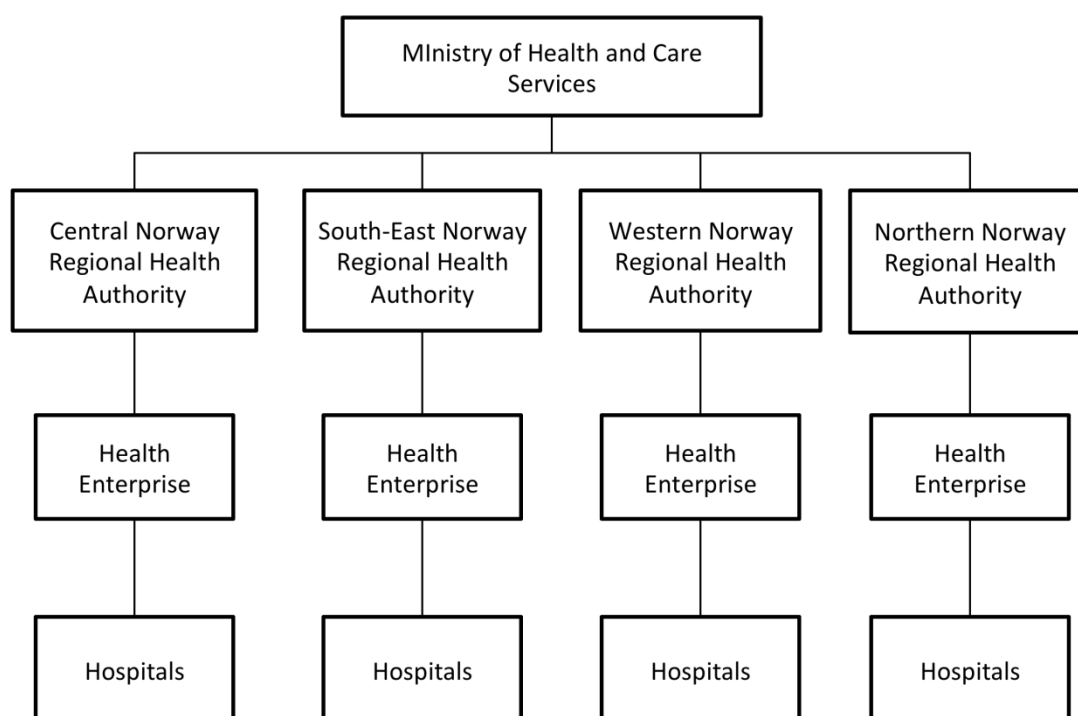


Figure 6: The structural organization of specialized care in Norway

(Adapted from Magnussen, Hagen, and Kaarboe, 2007)

The South-Eastern Norway Regional Health Authority is comprised of seven hospital regions (Figure 7) with ten hospital trusts, as reported by their website (Helse Sør-Øst, 2015). According to the South-Eastern Norway Regional Health Authority annual report from 2012, the area included 2.8 million residents, which accounted for 56% of the Norwegian population in 2012. The total revenue for the year was NOK65 billion, of which, NOK15.4 billion was activity-based financing (Helse Sør-Øst, 2012).

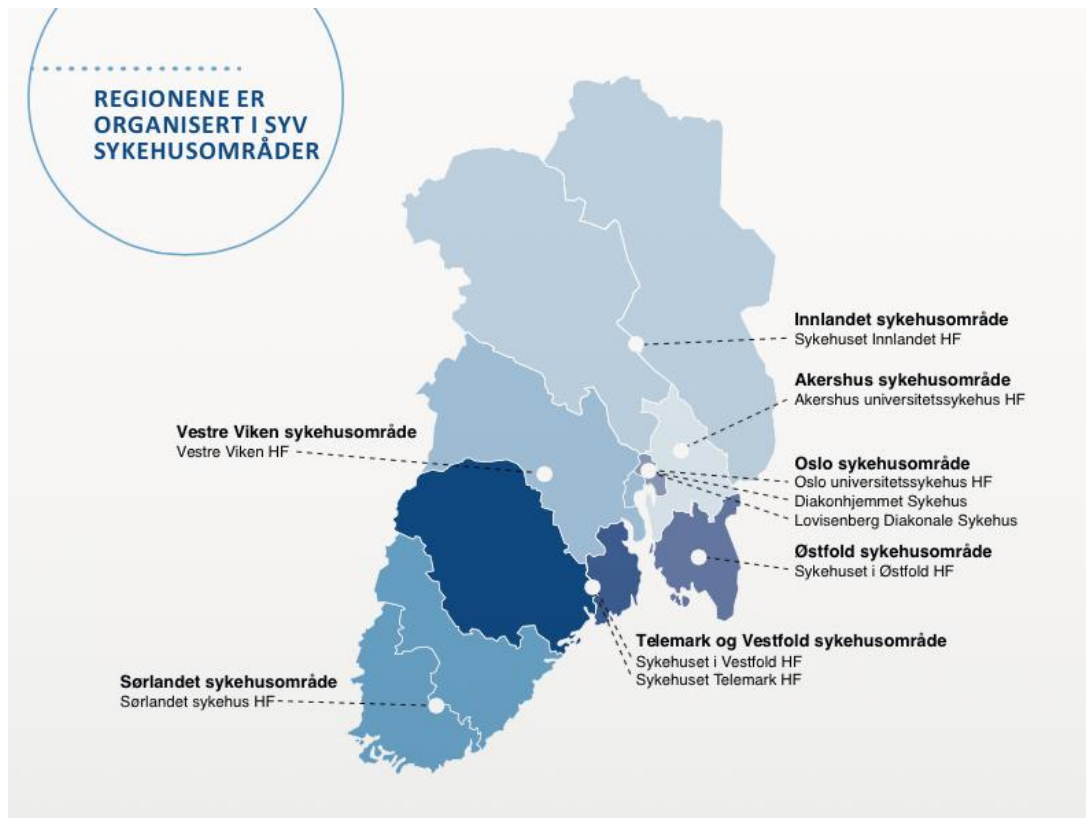


Figure 7: Map of the South-Eastern Norway Regional Health Authority with its seven hospital regions

(Helse Sør-Øst, 2012, p. 3)

With regard to primary health care, Johnsen (2006, p. 19) states that municipalities are responsible for funding and provision. This includes curative and preventative treatment like:

- “Promotion of health and prevention of illness and injuries, including organization and running school health services, health centres, child health care provided by health visitors, midwives and physicians.”
- “Diagnosis, treatment and rehabilitation.”
- “Nursing care within and outside institutions.”

1.3.2 Health care financing (A.E.S.A.)

Activity-based financing rooted in the Diagnosis Related Groups (DRG) system for somatic inpatient activity was first implemented in Norway in 1997 (Johnsen, 2006). The financing of the regional health authorities is from two sources: block grants and activity-based financing. The regional health authorities are responsible for the

distribution of funds to hospitals and other service providers (Norwegian Government, 2014). For the year 2012, the block grant made up 60% and activity-based financing made up 40%, for financing somatic hospitals in Norway. The basic funding of the regional health authorities is a yearly grant independent of the level of activity; instead, it is based on the number of inhabitants in the region and their age composition (Norwegian Government, 2014).

The DRG system is a method for classifying patients. Hospital stays or outpatient consultations in somatic institutions are classified into groups that are clinically and economically similar (Norwegian Directorate of Health, Activity-Based Financing, 2012). DRG codes classify medical cases according to primary and secondary diagnoses, patient age, gender and comorbidities, the procedures performed and complications, if any (Cylus and Irwin, 2010). Primary diagnosis is incorporated into the DRG that has been selected as the principal DRG for hospital reimbursement purposes (Figure 8). The selection of the principal DRG is done by a computer software and algorithm, meaning that hospitals and doctors cannot select which DRG code they would prefer to use for reimbursement purposes.

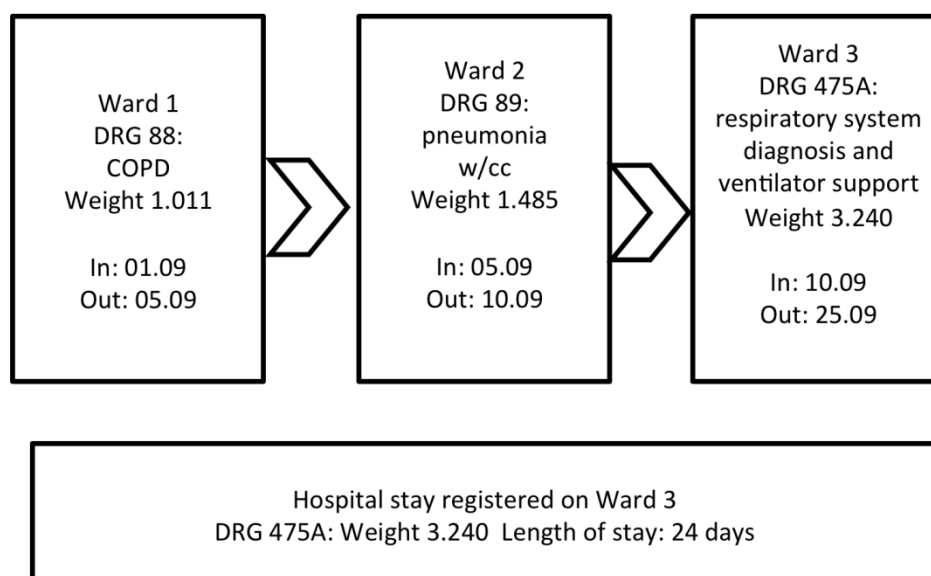


Figure 8: The aggregation of ward DRG codes to hospital reimbursed DRG
(Adapted from the Norwegian Directorate of Health, 2012)

Outpatient consultations generate lower DRG reimbursements than day patient consultations because outpatients are subject to a co-payment. This co-payment is deducted from the total cost when setting the DRG for outpatients, thus, resulting in lower DRG weights when compared to day patient DRGs (Norwegian Directorate of Health, 2012).

Over the years, government health care expenditure in developed countries has increased faster than their Gross Domestic Product (GDP) (National Bureau of Economic Research, 2005). These authors claim that this development must be seen in conjunction with country-specific age-health expenditure profiles, as demographics and the total number of beneficiaries have increased (Figure 9 and 10). The population size has increased in most countries, women's fertility has dropped and the share of the population that is elderly has increased in developed countries (Bongaarts, 2009). Health expenditure per capita tends to be associated with income per capita, which may explain why Switzerland and Norway had the highest figures in 2010, with spending above €4,000 per person, followed by the Netherlands (€3,890), Luxembourg (€3,607), and Denmark (€3,439) (Figure 11).

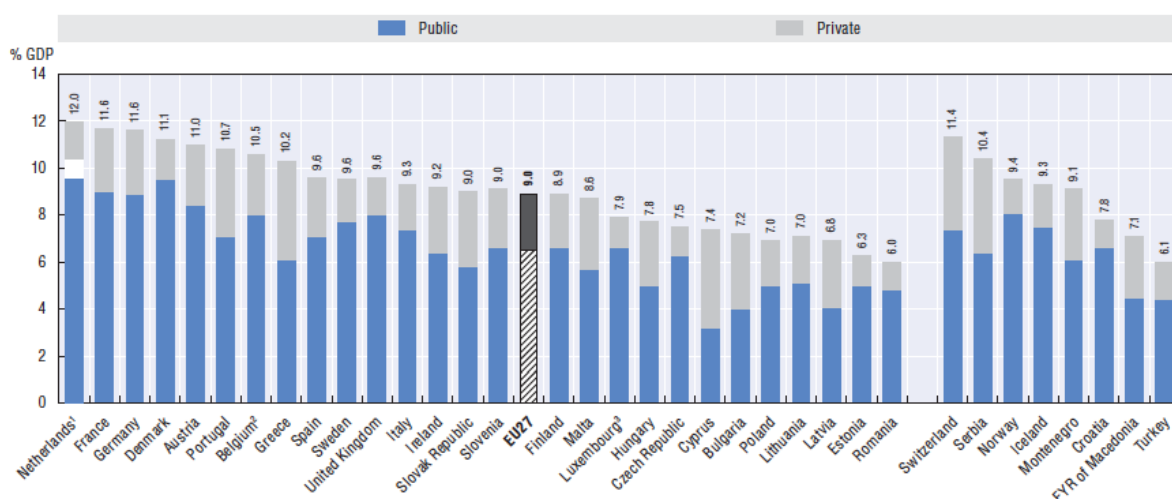


Figure 9:Total health expenditure as a share of GDP, 2010 (or nearest year)

(Organization of Economic Cooperation and Development, 2012, p. 123)

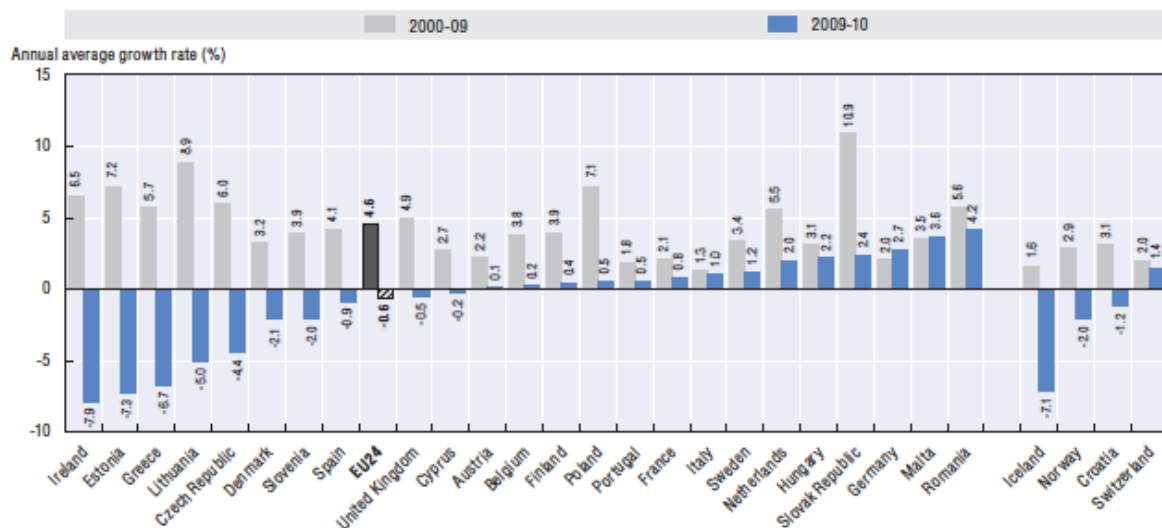


Figure 10: Annual average growth in health expenditure and GDP per capita, in real terms, 2000-2010 (or nearest year)

(Organization of Economic Cooperation and Development, 2012, p. 121)

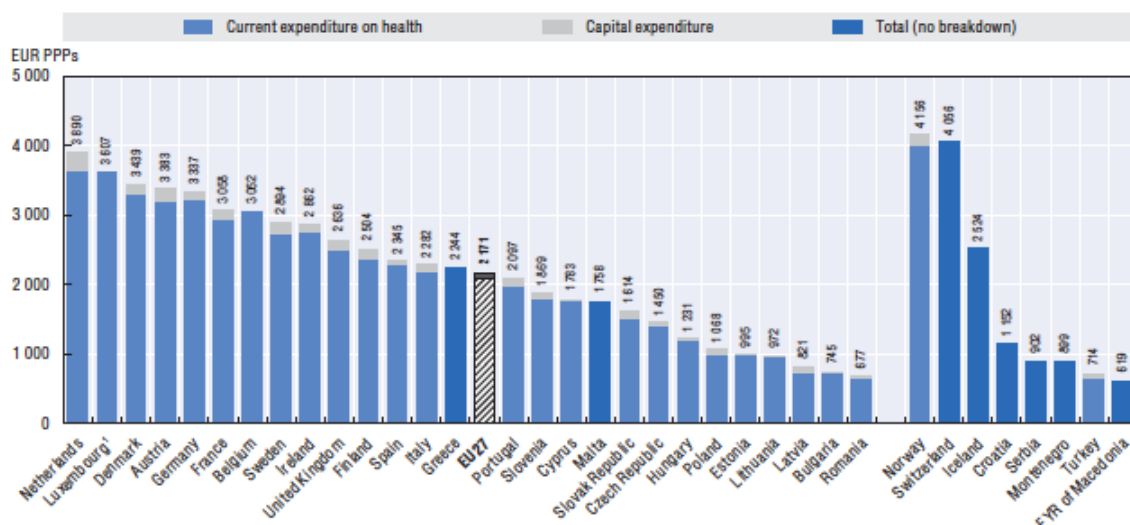


Figure 11: Health expenditure per capita, 2010 (or nearest year)

(Organization of Economic Cooperation and Development, 2012, p. 121)

1.3.3 Antibiotic resistance and MRSA in Norway (A.E.S.A.)

A joint report from 2012 by NORM, which is the Norwegian surveillance program for antimicrobial resistance in human pathogens, and NORM-VET, which is a monitoring program for antimicrobial resistance in animal pathogens and the food production sectors, says that in 2012, the consumption of penicillin for humans, measured in Defined Daily Doses, accounted for 41% of the total antibiotic use (NORM/NORM-VET,

2012). Over the years, although the total sale of antibiotics in Norway has remained stable, the sale of narrow-spectrum penicillin has decreased while broad-spectrum penicillin has increased (Norwegian Ministry of Health and Care Services, 2008).

The number of reported cases of MRSA infections and colonization in Norway between 2010 and 2012 deserves attention from the health authorities. According to the Norwegian Surveillance System for Communicable Diseases, the number of MRSA infections and colonizations reported in 2012 was 575 and 633 respectively, compared to year 2010 when 429 infections and 478 colonizations were reported. This is a 34% increase in the number of infections and 32% increase in the number of colonizations from 2010 to 2012. Although, these figures are still very modest compared to other non-Scandinavian countries, it is a negative development for Norway. Therefore, we must not only prevent and control the spread of MRSA, but we must also estimate the economic burden posed to the Norwegian health care system.

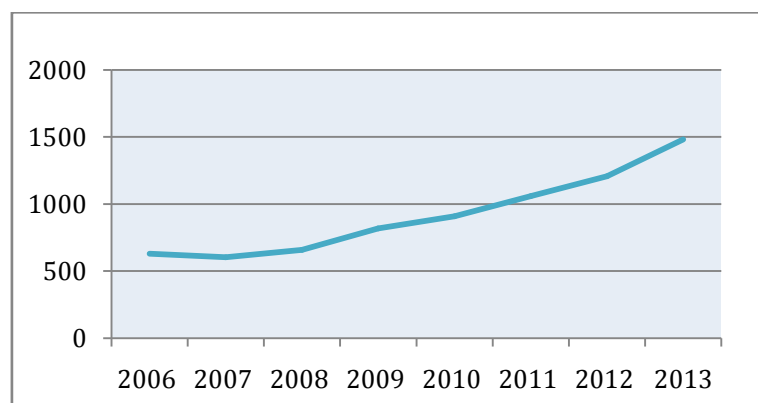


Figure 12: Infection and colonization with Methicillin-resistant *S. aureus* (MRSA) in Norway 2006-2013

(Norwegian Surveillance System for Communicable Diseases, 2015)

1.3.4 National guidelines and containment protocol (both authors)

In 2009, the Norwegian Institute of Public Health and the Norwegian Health Directorate published a manual that included specific measures to be taken to prevent an endemic presence of MRSA in the bacterial flora of Norwegian health institutions (Norwegian Institute of Public Health, 2009). These guidelines are well implemented at all levels of the health care system. There are important principles, anchored in Norwegian law, governing the actions taken to prevent and control the spread of MRSA in Norwegian health facilities:

- Suspected or confirmed MRSA colonization or infection must not delay necessary examination, treatment or care
- Measures against MRSA can only be taken with the patient's consent
- Measures against MRSA should not put limitations to the patient's life beyond the prevention and control measures taken when in contact with the health care system

Basic infection control routines are based on the principle that all bodily fluids, such as blood, secretions and excretions (except sweat), torn skin and mucous membranes, may contain infectious agents.

Hospitals: In this setting, there is an active “search and destroy” MRSA practice, meaning that they examine persons who may have an increased risk of having MRSA at admission or employment, as well as tracking all contacts had by a newly detected case of MRSA in the hospital. The spread of infection is controlled by isolation of MRSA positive patients, work restrictions for care personnel who test positive for MRSA, and sanitation of colonization. Patients are screened before hospital admission if they meet the following criteria:

- Previously tested positive, without subsequently having three negative tests
- Have clinical symptoms, chronic skin disorders or have had medical equipment put through their skin or mucous membrane in the last 12 months in a foreign health care facility

Or in the last 12 months:

- Been diagnosed MRSA (even with a negative test outcome)
- Lived with someone who is MRSA positive
- Been in close contact without protective equipment

Or in the last 12 months have been abroad and:

- Been admitted to a health care facility
- Received extensive treatment or an exam in a health care facility
- Worked as a health care worker
- Stayed in an orphanage or refugee camp

In addition, a MRSA test is taken of all who have clinical symptoms on their skin or bruise infection, chronic skin conditions or permanent medical equipment inserted through their skin or mucous membranes, and who have been outside of Scandinavia for more than 6 consecutive weeks during the last 12 months. An unexpected detection of MRSA may lead to examination of all health care personnel and all patients in a specific ward.

Patients who are suspected of having MRSA are preemptively isolated until laboratory results indicate otherwise. Of those who test positive as either colonized or infected during their screening, isolation protocol is applied for the remainder of their hospital stay. This includes isolating the patient to a single room and using infection control measures, such as, wearing surgical masks, gloves, and gowns each time health personnel enter the room. Isolation protocol may also be applied to patients who are particularly vulnerable of contracting an infection. After a patient is either discharged or transferred, the cleaning personnel follow an extensive disinfection protocol.

Persons with MRSA may be offered sanitation of colonization. Control tests are carried out one, two, and three weeks after sanitation. New control tests are recommended three, six, and twelve months after sanitation of MRSA.

2. Literature review (A.E.S.A.)

Several studies in Europe and the US have attempted to estimate the additional resource use (costs) associated with MRSA, and excess length of stay has been found to be a leading cause of increased costs for hospitals (Macedo-Viñas et al., 2013). Other studies have shown that there is an expected additional length of stay between 3-25 days for patients with MRSA as compared to patients with MSSA (Macedo-Viñas et al., 2013).

2.1 Previous studies (A.E.S.A.)

Although we believe increased resistance poses a huge burden on economies, there are currently few studies that establish the economic burden of MRSA diagnoses in Norwegian hospitals. Tri Chinh Nguyen from the University of Tromsø (2009) conducted a cost-effectiveness analysis of antibiotics used to treat MRSA infections, and his

objective was to establish which intervention was the most cost-effective, not to establish the economic burden of the disease.

Brith Christenson et al. carried out a study in 2011 on MRSA infections in Uppsala county in Sweden. In this study they identified MRSA clones originating in Sweden and outside of Sweden. The cost per identified case of HA-MRSA was SEK216,700, while the cost per case of CA-MRSA was SEK38,000, possibly indicating that the patients who acquire MRSA while in hospital are already very sick, and that the cost of isolation plays an essential part when estimating the economic burden of MRSA infections.

A Swiss study from 2013 by Macedo-Viñas et al., estimated the economic burden of MRSA infections at Geneva University Hospital by multiplying excess length of stay for MRSA infected patients with bed-day costs. The authors compared average length of stay of MRSA negative with MRSA positive patients, using multistate modeling, which means that they compared MRSA positive with MRSA negative, and then compared MRSA infections with MRSA colonizations. Their findings showed that MRSA infections produced an average excess length of stay of 11.5 days and additional cost of CHF800 per case per day (€663 in 2012), meaning approximately €7,625.

Most recently, in October 2014, Hübner et al. published a paper on MRSA attributed costs of hospitalized patients in Germany. Their aim was to assess the additional cost of MRSA management measures, as well as identify the main cost drivers from the hospital's perspective. This study was based on a single hospital and 182 patients. They arrived at an MRSA attributed cost of €8,673 per case, including hygienic measures and laboratory costs.

With respect to the prevalence of MRSA in Norway, a time series analysis by John F. Moxnes et al. (2013) has studied the trends of MRSA infections in Norway and concluded that the proportion of MRSA in relation to the total number of *Staphylococcus aureus* positive tests is increasing in Norway. This is also supported by the number of registered cases of MRSA in the Norwegian Surveillance System for Communicable Diseases, which may be a consequence of increased screening following the implementation of the national guidelines for handling MRSA.

2.2 Current situation (A.E.S.A.)

To our best knowledge, there are currently no studies estimating the economic impact of MRSA positive patients in Norwegian hospitals. Some studies have looked at

the cost-effectiveness of drugs used to treat MRSA infections (Nguyen, 2009) and the development in the number of MRSA cases in Norway (Moxnes et al., 2013). Our aim is to contribute to this field with our findings on costs related to extended hospital stays for patients through the analysis of data from the South-Eastern Norway Regional Health Authority from the year 2012.

3. Theory

3.1 Costs (C.J.)

When considering economic evaluation in health care, we must first define how we identify costs. The consumption of health care resources by one patient at some time and place means that at the same time and place, those health care resources are not available for another purpose. In other words, the consumption of health care resources has limits. The cost of care can thus be understood as the consumption of health care resources. The value of this resource, or the cost we assign to it, is the opportunity cost of the resource (Hunink, 2001). Put in other terms, it is the benefit that is forgone by not investing in the alternative health care treatment or program that those same resources could have been allocated to (Olsen, 2009).

The perspective of an economic evaluation will determine how we define opportunity cost. Various perspectives that may be considered include societal, hospital, governmental, and that of the insurer. The types of costs that may be accounted for will also depend on the perspective from which the analysis is done. From a hospital perspective, the costs of health care resources are most important, and within that category, the time of health care personnel is most significant (Hunink, 2001). Other non-health care resource costs that may be accounted for in an analysis performed from the societal perspective include transportation for patients, the patient's time, caregiver's time, and the productivity lost by the patient being unable to work, among other costs. Within each perspective there are two levels of costs to consider, gross-costing and micro-costing. Gross-costing includes an existing set of prices, such as, the DRG reimbursement rate. Micro-costing accounts for inputs of service and retrieving data on price per unit, so that a cost estimate can be calculated (Hunink, 2001). For example, the cost per unit of sterile gowns worn by hospital staff when they enter rooms where this protocol applies may be multiplied by the number of units used to find the micro-cost of gowns.

After the perspective is defined and types of costs and level of costing are decided, understanding the difference in average versus marginal costs becomes imperative when considering decision making of health care resource distribution. To calculate the average or the marginal cost, a distinction that needs to be made is the difference between fixed costs and variables costs. In his book, *The Principles in Health Economics and Policy*, Jan Abel Olsen clarifies the difference between fixed and variable costs. The costs of a hospital building or machinery are considered fixed input factors and are termed fixed costs, since they are not dependent on a health care facility's level of productivity. Inversely, the variable costs may change based on productivity. Such costs would include labor hours and medical supplies (Olsen, 2009). Olsen then explains the calculation of total cost (TC) as the fixed costs (FC), added to the variable costs (V); with the variable costs being multiplied by the quantity (X) used i.e. number of labor hours (Olsen, 2009, p. 196).

The formula Olsen (2009) provides for calculating total cost is:

$$TC=FC+V (X)$$

To calculate the average costs (AC) Olsen (2009) provides the following:

$$AC=TC/X$$

The marginal costs (MC) "...are the additional costs following a one-unit change in production" (Olsen, 2009, p. 196). To calculate the marginal costs Olsen (2009) gives the formula:

$$MC=V (X+1)-V (X)$$

Using marginal costs is the general rule for economic evaluations that include priority setting regarding health care resource distribution (Hunink, 2001). Olsen (2009) illustrates the significance of this distinction by citing the Neuhauser and Lewicki study from 1975 of the costs of guaiac stool testing. To detect bowel cancer, six sequential tests were recommended by medical specialists. The study found that the average cost of the six tests was \$2,451 per cancer detecting test. When considering that the incremental detection rate decreased heavily with each test, they found that the marginal cost for the sixth test detecting cancer was \$47 million (Olsen, 2009). This example is quite extreme, but one can also understand practically that the first day in the hospital for a hip replacement surgery is going to be much more expensive than the

day of discharge. Thus, when informed decisions are to be made about health care resource allocation, marginal cost must be used rather than average costs.

3.2 Economic Evaluation(C.J.)

Economic evaluation has theoretical basis in welfare economic theory, which infers that decisions regarding health care expenditures should be regarded in the same way as non-health care related expenditures. What is of interest in decision making in welfare economic theory is whether or not a change in resource allocation represents a Pareto improvement in social welfare (Briggs et al., 2006). Pareto improvement is defined as, “a policy that makes one or more persons better off and makes no person any worse off” (Drummond et al., 2005, p. 217).

According to Drummond et al. (2005, p.7), there are two questions of interest in economic evaluations.

1. “Is this health procedure, service, or programme worth doing compared with other things we could do with these same resources?”
2. “Are we satisfied that the health care resources (required to make the procedure, service, or programme available to those who could benefit from it) should be spent in this way rather than some other way?”

There are two important features that characterize economic evaluation analysis. The first is that it incorporates both costs and consequences. The second is that economic evaluation is concerned with choices. These two features define economic evaluation as, “the comparative analysis of alternative courses of action in terms of both their costs and consequences” (Drummond et al., 2005, p. 9). The three primary forms of analyses in economic evaluation are cost-effectiveness analysis, cost-benefit analysis, and cost-utility analysis. The distinguishing feature of each is how they measure consequences or outcomes. Cost-effectiveness analysis compares costs in relation to a common outcome, such as life-years gained, which may be different in consequence between different programs. Cost-benefit analysis translates outcomes into monetary units and compares costs. Finally, cost-utility analysis measures outcomes in terms of utility, such as health-related quality of life (Drummond et al., 2005).

Although we will not be performing decision analysis, our cost analysis of MRSA will be based in our disciplinary foundations of economic evaluation rooted in welfare

economic theory. It is from within framework that we will assess the cost burden of MRSA. As we are not performing decision analysis, our results are not recommended for priority setting. Rather, they may be considered as a reference for future economic evaluations.

3.3 Principal-Agent Theory(C.J.)

The Principal-Agent Theory can be used as a framework to define how the Norwegian health system works. Principal-Agent Theory provides a flexible framework for modeling variations in institutional arrangements and comparing their potential to generate the desirable behavior by the agents (Gailmard, 2012). Briefly accounted, the principal must produce an incentive scheme that leads the agent to choose the principal's preferred action. This influence fails in relationships where there is information asymmetry, meaning that one party possesses information that the other party does not, such as the agent having more information than the principal. It also fails where there is moral hazard, which means that the agent would choose a series of actions normally considered inappropriate if the payment scheme puts all the risk on the principal (Miller, 2005).

Within health care, the principal-agent relationship is between the patient as the principal, and the physician as the agent. Physicians in this relationship are always expected to apply their expertise and skills to the betterment of the principal's health, and never to their disadvantage (Zweifel et al., 2009) In reality, physicians have more knowledge and power than patients when it concerns making informed decisions about medical care, hence, there is information asymmetry in the patient-physician relationship. As a consequence, within health care systems, a third party is introduced to offset the conflict of interest between the patient-physician relationship. This third party is referred to as a complementary agent, and is usually represented by either an insurer or policy maker (Zweifel et al., 2009).

In the Norwegian national insurance scheme, this is the policy maker's role. The two main tasks of a complementary agent are to ensure quality and negotiate remuneration. This third party is meant to resolve the conflict of interest between the patient and the physician (Zweifel et al., 2009). The diagram below, borrowed from Zweifel et al., is a depiction of this relationship.

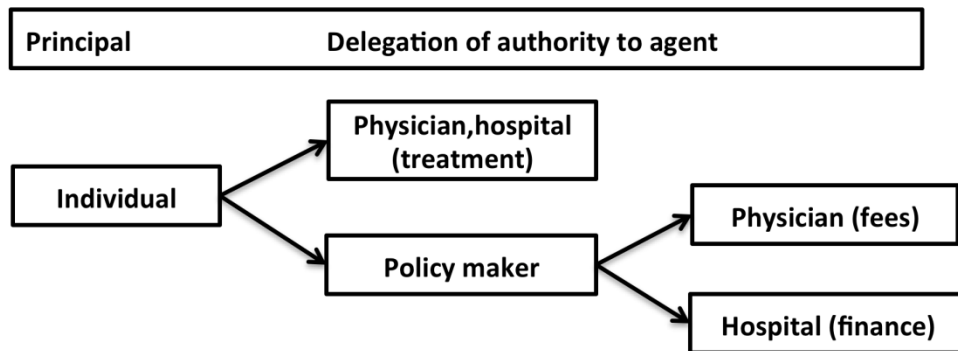


Figure 13: Principal-agent relationship in the Norwegian national insurance scheme
(Adapted from Zweifel, 2009, p. 380)

When considering the economic burden of MRSA in hospitals in light of the principal-agent relationship, we can better understand the advantages of knowing the costs associated with MRSA. Policy makers hope to ensure that there is no disincentive for hospitals to act in the best interest of the patient. The cost burden of MRSA is important to define for not only the hospitals treating these cases, but also for the overall health care budget and society.

3.4 DRG payment systems (A.E.S.A.)

The prospective DRG based payment system was originally introduced in the United States in the late 1970s when policy makers were forced to radically reform Medicare in order to avoid insolvency for the program (Mayes, 2007). Until then, Medicare had reimbursed hospitals whatever they charged for treating Medicare patients. This situation changed with the introduction of the DRG, under which system Medicare paid hospitals a predetermined amount based on the patients diagnosis (Mayes, 2007).

DRG based payment systems were eventually introduced in a number of countries. The main objectives of these systems were cost containment, to increase efficiency, or to improve transparency in hospital activities (Mathauer and Wittenbecher, 2013).

Norwegian regional health authorities, which are in charge of administering funds to hospitals, receive a fixed share of 60% of their income from the government

while 40% is activity-based financing through DRGs. There is currently no systematic method for accounting for the additional cost of MRSA. When a hospital receives a MRSA colonized or infected patient, it faces a dilemma when choosing to treat the patient in the hospital and incur the potentially high costs of a lengthy stay in isolation, or to send the person home. The latter alternative would allow the hospital to prevent potential spread of MRSA, save costs, and at the same time be able to offer hospital beds to other patients, increasing the hospital's activity.

The activity-based reimbursement to Norwegian hospitals was 40% of the total estimated costs in 2012 (Norwegian Directorate of Health, 2012). According to S.O. Petersen (2010), this offers a strong incentive for the hospitals to maximize the patient volume and hence the number of DRG points. Petersen also notes that the mean length of stay at Norwegian hospitals has been decreasing annually, from 5.67 days in 2002 to 4.75 days in 2008. At the same time, the readmission rate has increased by roughly 15%. In theory, this decrease in the length of stay and increase in readmissions can be explained by the imbalance in the principal-agent relationship, as well as the complementary agent's lack of knowledge to offset the balance.

Perencevich et al. (2007), in their article titled, "Raising Standards While Watching the Bottom Line: Making a Business Case for Infection Control," make a strong case for the need to ensure infection control measures are financially incentivized. In the United States, which is the context the authors are writing from, infection control programs are often seen as areas where there is potential for budget cuts. The authors encourage high quality cost-effectiveness evaluations when hospital administrators are making decisions regarding infection control. The foundation for a cost-effectiveness analysis is obtaining data on incidence rates and attributing costs to those incidences. We hope that our cost analysis will serve to encourage a proper cost-effectiveness analysis so that informed decision-making is possible.

4. Objectives and Hypothesis (both authors)

The overarching objective of this study was to estimate the costs associated with the patients diagnosed with MRSA who received specialized care, and to characterize this patient population using data from the South-Eastern Norway Regional Health Authority as reported and registered in Norwegian Surveillance System for Communicable Diseases and the Norwegian Patient Registry during the year 2012. This

was done by finding the mean length of stay per hospital admission for MRSA diagnosed inpatients compared with non-MRSA inpatients. In addition to length of stay, the average reimbursement based on the DRG cost weight and the average number of subsequent episodes of care, were used as proxies for resource use.

We hypothesized that MRSA inpatients have a longer length of stay on average than non-MRSA inpatients, and that they also have more episodes of care and are more costly based on their DRG reimbursement amount.

Our aim was to address the following questions:

- What are the characteristics of patients with MRSA in terms of age and gender?
- How many subsequent episodes of hospital admission did MRSA patients have on average in 2012?
- Do patients diagnosed with MRSA have lengthier stays in the hospital compared with non-MRSA patients?
- What is the average DRG based reimbursement amount for MRSA patients at all levels of specialized care (inpatient, outpatient, day patient)?
- Are there any particular characteristics that distinguish this sample population or could bias our findings?

5. Methods

5.1 Study design and data (both authors)

This was a register-based case-control study using data for 2012. The data in our analyses stemmed from two sources: the Norwegian Patient Registry and the Norwegian Surveillance System for Communicable Diseases. The linkage of these data sets was the result of a pilot program run by the Norwegian Institute of Public Health from 2012, and was restricted to the South-Eastern Norway Regional Health Authority (Helse Sør-Øst). These data were intended to create a dynamic disease model displaying the spread of MRSA within hospitals. Thereafter, the Ministry of Health and Care Services requested a cost analysis to be done with these data. This project was meant to test methodological approaches for future cost analyses of MRSA at the Institute of Public Health.

In order to estimate the costs associated with patients suffering from MRSA infection, it is important to distinguish between colonization and actual infections (clinical disease), because colonization of the MRSA bacterium may not need in-hospital care until another underlying condition weakens their immune system and sets the

proper conditions for the bacterium to cause harm. An infected person, on the other side, is usually already sick and may have gotten the infection in hospital. Given the challenges posed by an MRSA infection, this will probably result in a higher cost per case of MRSA infection than MRSA colonization. However, for the purpose of our analysis from a hospital perspective, colonization and infection have been treated equally as MRSA positive, as the guidelines for treating both colonized and infected patients are the same.

5.2 Norwegian Surveillance System for Communicable Diseases

(A.E.S.A.)

The Norwegian Surveillance System for Communicable Diseases (MSIS) is run by the National Institute of Public Health. Microbiological laboratories that analyze specimens from humans, as well as all doctors in the country, are required by law to notify cases of certain diseases to this central surveillance system (Norwegian Surveillance System for Communicable Diseases, 2015). Therefore, information from MSIS is generated through compulsory reporting of all notifiable diseases detected in Norwegian inpatient and outpatient facilities. All patients reported with MRSA infection or colonization status (among other diseases) to the Norwegian Institute of Public Health, have been registered in the MSIS database since 1995 (Norwegian Institute of Public Health, 2010). Patients are diagnosed with MRSA through microbiological laboratory testing of samples taken from various sites of the body including the throat, nares, perineum, fresh scars/skin lesions/wounds/eczema, and insertion sites of catheters. There is no registration of clearance of MRSA.

MSIS has existed nationwide since 1975, but in 2003 legislation granted more authority and responsibility to the surveillance system as a response to increasing challenges in infectious disease control (Norwegian Institute of Public Health, 2007).

The variables of interest from MSIS were:

- MRSA test result
- MRSA test date
- Diagnosis of colonization or infection
- Ethnicity
- Country of birth

5.3 Norwegian Patient Registry (A.E.S.A.)

The Norwegian Patient Registry (NPR) is the national registry of patients who are waiting for or have received care at the specialist health care level. The registry was created in 1997, but personal ID numbers for each episode of care were not added until 2008 (Norwegian Directorate of Health, 2015). The data are encrypted, meaning that information such as patient name and personal identity number are not stored in this registry. The main objectives of the NPR are:

- To serve as foundation for administration and quality assurance of specialist health care services, as well as activity-based financing
- To contribute to research
- Serve as a basis for the creation of new disease and quality registries
- Contribute with information that may prevent accidents and injuries

The variables of interest from NPR were:

- Age
- Gender
- Type of episode of care (inpatient, outpatient, day patient)
- Primary diagnosis
- DRG code
- DRG cost weight
- Date of admission, date of discharge
- ID of hospital and ward

In the appendix, Table 4 is a list of the variables from both NPR and MSIS that were relevant for our research.

The data set for our analysis included the patients diagnosed with MRSA and their episodes of care at the specialist level. The data also included all of the patients in the South-Eastern health region who had received specialist care for the year during the period January 1, 2012 to December 31, 2012. The unit of observation was the episode of care defined as inpatient, outpatient, or day patient care, with specialist care at a hospital. The total number of episodes of care was 3,501,484. The total number of individual patients was 984,266.

The patients of interest were those diagnosed with MRSA either before they received care from the hospital or while they were in hospital. The total number of patients in the NPR data set that met this criterion was 315. Patients who were diagnosed with MRSA after they had received hospital care (n=234) were excluded. The total number of episodes of care for these 315 patients was 961. These episodes encompassed inpatient admissions (n=174), outpatient care (n=241), or day patient care (n=20). The primary group of analysis among the 315 patients consisted of the 174 patients who received inpatient care. Variables of interest for this group were their length of stay in hospital and the hospital reimbursement amount based on the DRG cost weight, as well as the number of inpatient admissions subsequent to their initial admission registered in our data.

5.4 Data cleaning (C.J.)

Petter Elstrøm of the Norwegian Public Health Institute, in collaboration with the authors, did the cleansing of these data to prepare for analyses. After the linkage of the MSIS and NPR data sets, five records with missing identification numbers were excluded. There were no other inconsistencies, incorrect, or incomplete records that needed cleansing. Patients who were registered with MRSA in MSIS but did not receive specialist care, thus not registered in NPR, were excluded. Character variables were converted into numeric variables. There were inconsistencies in the way individual hospitals applied code numbers for each ward. For example, the gynecological wards at different hospitals had different ward codes. Recoding was required to identify type of wards in each hospital, and to create consistent codes for identical wards for the entire health region.

5.5 Statistical analysis (C.J.)

We carried out a cost analysis of MRSA diagnosed patients. Cost of illness analyses involves the identification, measurement and valuing of resources related to an illness (European Centre for Disease Prevention and Control, 2009). All statistical analyses were performed in Stata Statistical Software (StataCorp, 2013). Simple descriptive statistics were presented as proportions and means. Estimation of cost was performed by comparing MRSA patients with matched non-MRSA controls. The ratio of matched cases to controls aimed to be 1:4. We applied the resampling method of

bootstrapping 1000 times to derive 95% confidence intervals (CI) for both cases and controls.

5.6 Comparing costs of patients with and without MRSA (both authors)

We had three measures to evaluate costs: DRG based cost per episode of care, length of stay, and the number of episodes of care subsequent to the first episode. The DRG codes in the data set were the basis for hospital reimbursement and were used as a reference for costs. Within-hospital transfers to different departments/wards were not counted as an episode of care unless the date for the transfer was not included in the in-out period. Matching cases to controls was based on the cases' first episode of care that met the matching criteria (see Table 1).

To evaluate costs, the cases were matched to controls from the remaining patients in the data set who were non-MRSA patients (n= 983,951). In total, six matched control groups were generated. The first matched control group (MC1) was comprised of non-MRSA diagnosed inpatients and was used as control group for MRSA diagnosed inpatients (n=174). The matching criteria for this group were: inpatient status, age, gender, month of hospital admission, primary diagnosis related to the reimbursement DRG code, and hospital group. With hospital group we referred to institutions offering the same type of services, such as somatic hospitals, rehabilitation, palliative hospitals, among others. The dependent variable of interest (the proxy for cost) was the hospital reimbursement amount based on the DRG code and weight.

The second matched control group (MC2) was also comprised of non-MRSA diagnosed inpatients, and was also used as a control for MRSA diagnosed inpatients (n=174). The main distinction between MC1 and MC2 was that the MC2 criteria included matching based on the DRG reimbursement code and did not include primary diagnosis. All other matching criteria were the same. The dependent cost variable of interest in this matched control was the difference in length of stay.

As a third level of comparison of treatment costs of patients with and without MRSA, we also carried out the matching of cases (n=174) with controls (non-MRSA patients) based on age, gender, month of first care-episode, inpatient status, and ward. The ward codes in our data set incorporated the health trust, hospital, and the ward to which the patient was admitted. With this information, we believed that it would be possible to capture similar patients while at the same time avoiding matching on too

specific and similar criteria such as the primary diagnosis and DRG. The cost variables of interest in this matched control group were: length of stay, hospital reimbursement amount based on the principal DRG, and the number of subsequent episodes of care.

The fourth matched control group (MC4) was used as a control for MRSA diagnosed patients (n=315), and included non-MRSA diagnosed patients. The matching criteria were: age, gender, ward of treatment, and month of treatment. The dependent variable of interest was the number of subsequent episodes of care at all levels of care (inpatient, outpatient, or day patient).

The fifth and sixth matched control groups (MC5 and MC6) were used as controls for MRSA diagnosed outpatients (n=241) and MRSA diagnosed day patients (n=20) respectively. These control groups consisted of non-MRSA patients who received outpatient care (MC5) and non-MRSA patients who received day treatment at a somatic institution (MC6). The matching criteria for MC5 were outpatient status, age, gender, ward, and month of treatment, while for MC6 we matched based on day treatment status, age, gender, ward, and month of treatment. The dependent variables of interest in these matched control groups were the mean number of subsequent episodes and the hospital reimbursement amount based on DRGs.

The matching criteria aimed to create comparable groups that had similar characteristics except for the MRSA status. All of the matching criteria were used in an attempt to control for confounding. Month of hospital admission or care was a criterion for matching since our data were from one year rather than a longer time span. This meant that patients with MRSA observed from the time they were diagnosed and in contact with specialist care were matched with non-MRSA patients based on the month of the MRSA patient's diagnosis. Thus, a patient diagnosed with MRSA and in contact with specialist care in November was matched with a non-MRSA patient who received specialist care in November. The variables of interest were then observed for the months of November and December. The matching criterion of DRG code was used to compare differences in length of stay, as DRG codes place patients in clinically similar groups and each DRG code has an average anticipated length of stay incorporated into the reimbursement algorithm. Matching on primary diagnosis was also an attempt at comparing patients with similar severity of illness. Since MRSA status is not incorporated into the DRG classification or primary diagnosis, matching on ward was an attempt to control for overmatching based on primary diagnosis and DRG.

The ratio of cases to controls aimed to be 1:4. The matched patients were taken from the NPR and restricted to patients from the South-Eastern Norway Regional Health Authority. The flowchart below shows the groups of analysis.

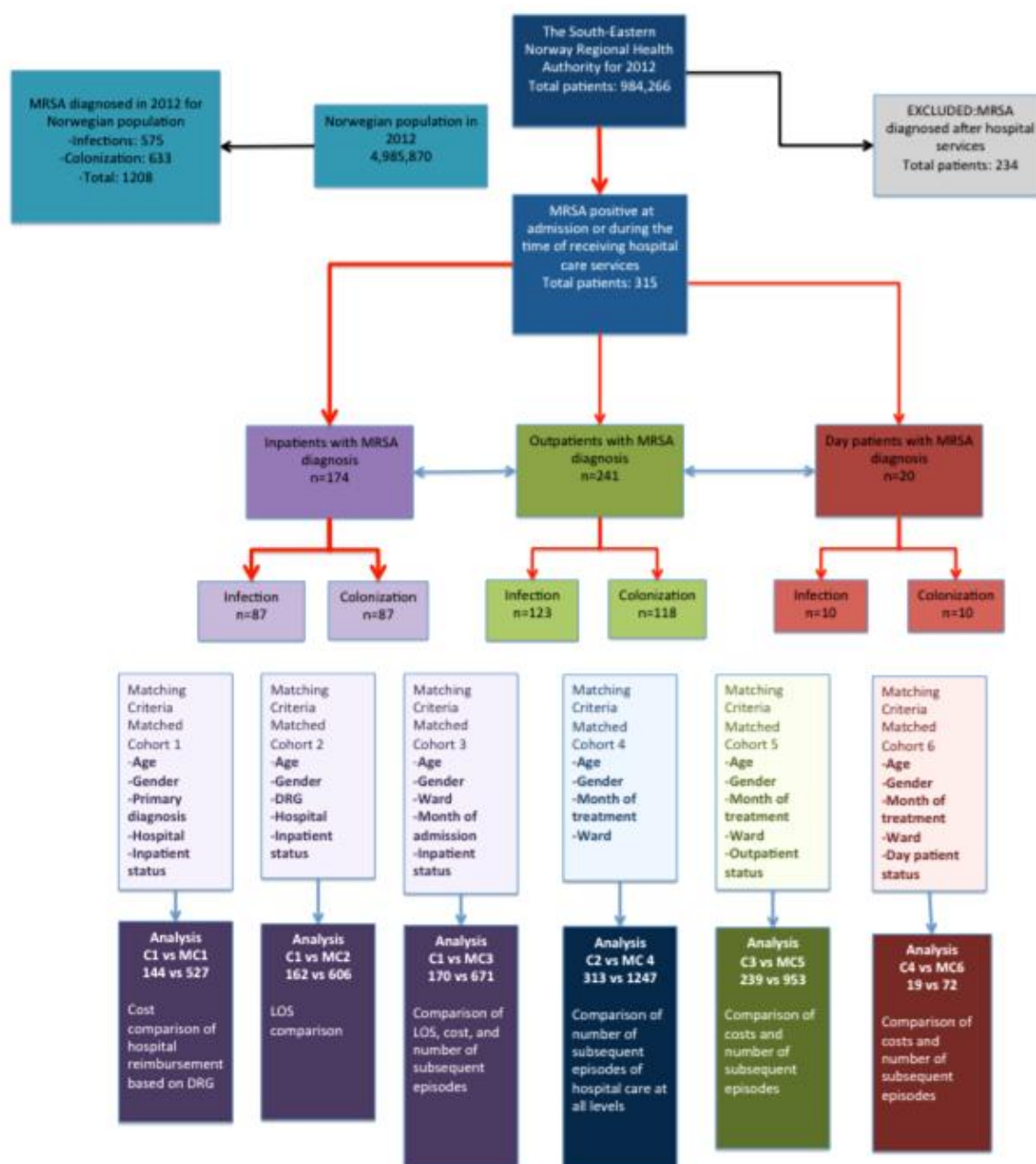


Figure 14: Groups of analysis

Table 1: Groups of analysis and matching criteria

Groups	Description	n
Group 1 (C1)	MRSA diagnosed inpatients	174
Group 2 (C2)	Total MRSA diagnosed patients at all levels of hospital care	315
Group 3 (C3)	MRSA diagnosed outpatients	241
Group 4 (C4)	MRSA diagnosed day patients	20
Matched Group1 (MC1)	Non-MRSA inpatients, match based on primary diagnosis at admission	4 to 1
Matched Group2 (MC2)	Non-MRSA inpatients, match based on DRG reimbursement	4 to 1
Matched Group3 (MC3)	Non-MRSA inpatients, match based on ward	4 to 1
Matched Group4 (MC4)	Non-MRSA patients, at all levels of care match based on ward	4 to 1
Matched Group5 (MC5)	Non-MRSA patients, outpatients match based on ward	4 to 1
Matched Group6 (MC6)	Non-MRSA patients, day patients match based on ward	4 to 1
MC1 matching criteria	MC2 matching criteria	MC3 matching criteria
Age	Age	Age
Gender	Gender	Gender
Month of admission	Month of admission	Month of admission
Primary diagnosis	DRG reimbursement	Ward
Hospital	Hospital	Inpatient status
Inpatient status	Inpatient status	
MC4 matching criteria	MC5 matching criteria	MC6 matching criteria
Age	Age	Age
Gender	Gender	Gender
Month of admission	Month of admission	Month of admission
Ward	Ward	Ward
	Outpatient status	Day patient status

5.7 Cost of additional days in hospital (C.J.)

The cost of additional length of stay (LOS) was calculated by estimating the mean LOS for all the non-MRSA diagnosed inpatients in the data set, then calculating the difference in LOS between the MRSA diagnosed inpatients (n=174) and the non-MRSA diagnosed mean. The DRG codes have nine aggregate categories for reimbursement: basic overhead (administration, etc.), nursing care, intensive care, operations, radiation therapy, imaging services, laboratory services, chemotherapy, and implants. Each DRG code has a percentage per category by which the total hospital reimbursement is divided. In an attempt to not overestimate the additional cost per day by including all of the categories, we multiplied the percentage weights per DRG for the categories of overhead costs, nursing care costs, imaging services, and laboratory costs. The sum total

percentage of these categories was then multiplied by the DRG reimbursement and then divided by the mean LOS for non-MRSA inpatients to calculate an average cost per day for the four categories per DRG code. This amount was then multiplied by the excess LOS for the MRSA patients.

6. Results

6.1 Patient characteristics - Sample of MRSA positive (n=315)

(A.E.S.A.)

All patients who received specialist health care during year 2012 as registered in the NPR were included in this study. The groups of analysis consisted of patients who had an MRSA diagnosis prior to or while undergoing hospital care. Patients who received their MRSA diagnosis after discharge from the hospital or who were not known MRSA positive at the time of hospital care have not been included. A total of 315 patients met the inclusion criteria, either as colonized (150 cases) or infected (165 cases).

The majority of patients (171) were females, making up 54% of the study population while 144 (46%) were males. The mean age for the 315 MRSA positive patients was 50 years. Most MRSA patients (60%) were younger than 50 years of age (Figure 15 and Table 2) among which 129 (41%) were aged 20 to 49. With respect to place of birth, 55% of the colonized and 69% of the infected were born in Norway, while the general Norwegian population consists of 89% born in Norway. All hospitals comprised in the South-Eastern Norway Regional Health Authority have rendered services to MRSA positive patients during year 2012 (Figure 16), and the hospitals serving the largest populations are also the ones with the highest number of MRSA cases.

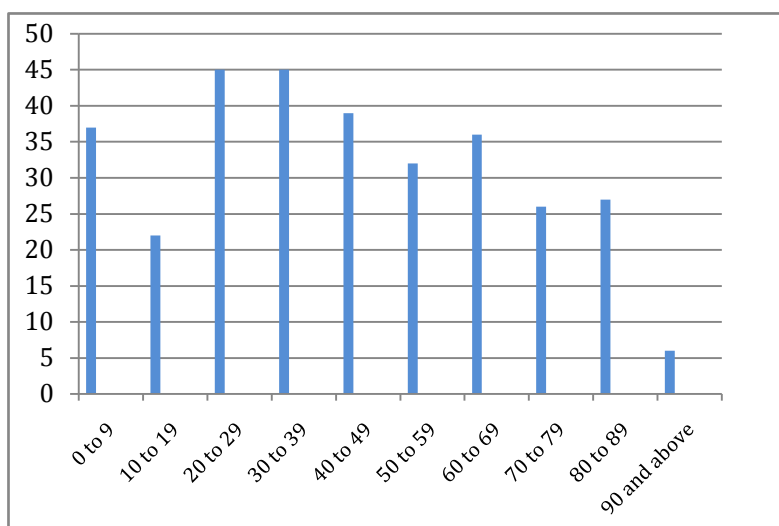


Figure 15: Age distribution of MRSA positive patients (n=315)

Table 2: Individuals identified with MRSA (n=315), according to age and gender, compared to the general Norwegian population of 2012

Characteristic	Infection n = 165	Colonization n = 150	Total n = 315	Norwegian population n= 4 985 870
Gender				
Female	86 (52 %)	85 (57 %)	171 (54 %)	2 498 871 (50 %)
Male	79 (48 %)	65 (43 %)	144 (46 %)	2 486 999 (50 %)
Age groups				
0 to 9	12 (7 %)	25 (17 %)	37 (12 %)	611 836 (12 %)
10 to 19	14 (8 %)	8 (5 %)	22 (7 %)	636 729 (13 %)
20 to 29	24 (15 %)	21 (14 %)	45 (14 %)	652 787 (13 %)
30 to 39	19 (12 %)	26 (17 %)	45 (14 %)	677 174 (14 %)
40 to 49	22 (13 %)	17 (11 %)	39 (12 %)	725 007 (15 %)
50 to 59	19 (12 %)	13 (9 %)	32 (10 %)	628 176 (13 %)
60 to 69	20 (12 %)	16 (11 %)	36 (11 %)	535 253 (11 %)
70 to 79	17 (10 %)	9 (6 %)	26 (8 %)	297 325 (6 %)
80 to 89	16 (10 %)	11 (7 %)	27 (9 %)	181 642 (4 %)
90 and above	2 (1 %)	4 (3 %)	6 (2 %)	39 941 (1 %)
Mean age (Std. Dev.)	53 (26)	48 (24)	50 (25)	
Ethnicity				
Born in Norway	114 (69 %)	83 (55 %)	197 (63 %)	4 439 138 (89 %)
Born abroad	51 (31 %)	67 (45 %)	118 (37 %)	546 732 (11 %)

(MSIS and Statistics Norway, 2012)

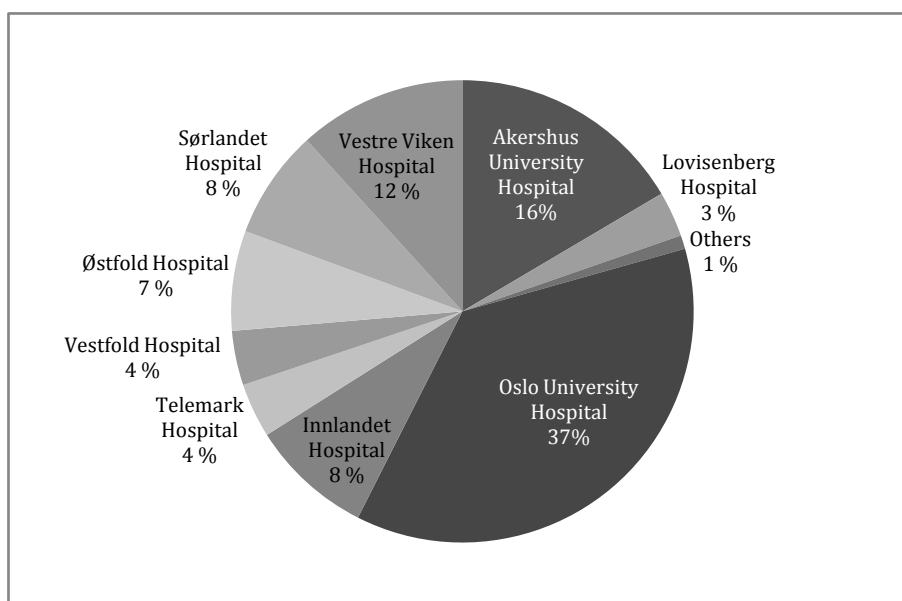


Figure 16: The MRSA patients (n=315) according to hospital

6.2 Patient characteristics - Sample of inpatients (n=174) (A.E.S.A.)

A subsample of 174 patients, consisting only of patients who received care services in the hospital (inpatient care) and who were known MRSA positive according to the criteria stated before, made up our primary group of analysis. Among the 174 inpatients, 87 cases were colonization and 87 were infection. In total, 88 (51%) were males.

Age distribution showed that the number of patients aged 10-19, 70-79, and 90 and above was lower than in other age groups. Patients less than 50 years of age made up 51% (88 patients) of the total. The most notable differences in age observed between the colonized and the infected patients, was in age group 0-9 year olds, constituting 14% of the colonized and only 9% of infected; as well as 30-39 year olds, comprising 15% of the colonized patients and only 7% of infected. The mean age of the 174 inpatients was 47 years of age.

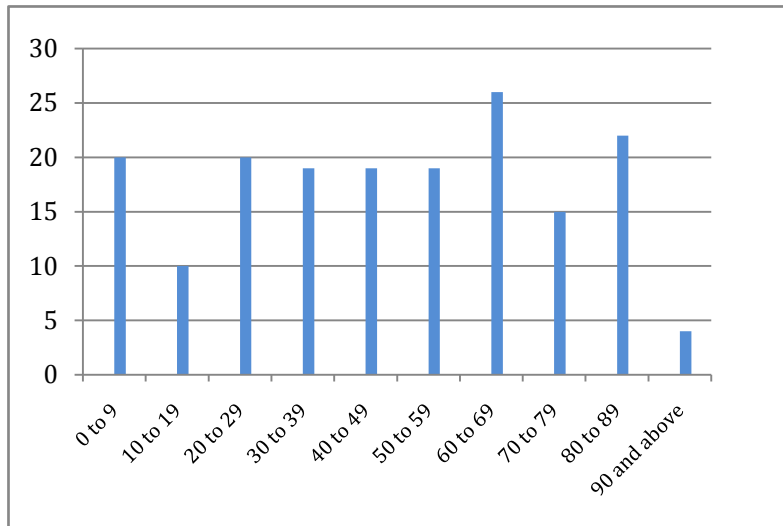


Figure 17: Age distribution of inpatients (n=174)

The two hospitals in the South-Eastern Health Region that had the most cases of MRSA positive patients were Oslo University Hospital which serves more than half a million inhabitants, with 52 MRSA diagnoses constituting 30% of our sample, and Akershus University Hospital, with 33 MRSA diagnoses constituting 19% of our sample (Figure 18). Oslo University Hospital is a highly specialized hospital offering services to the citizens of Oslo, as well as handling extensive regional and national tasks (Oslo University Hospital, 2015). It had approximately 1500 beds for somatic services in 2012. Akershus University Hospital moved into new facilities in October 2008. It is a somatic hospital and serves approximately half a million inhabitants in Follo, Romerike, Roemskog and the three northernmost districts in Oslo (Alna, Grorud and Stovner) (Akershus University Hospital, 2015). This hospital had approximately 700 beds for somatic services in 2012.

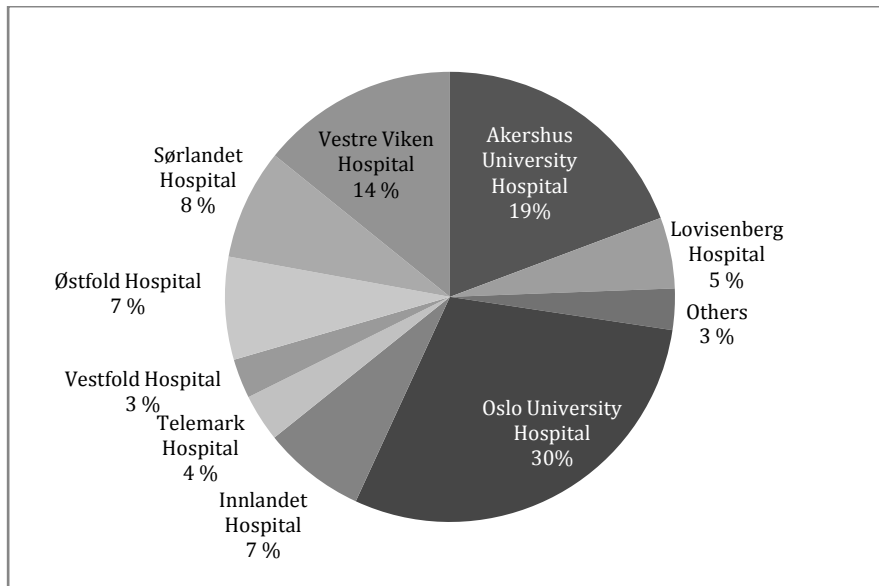


Figure 18: Inpatients (n=174) according to hospital

6.3 Cost analysis based on matched groups

6.3.1 DRG based reimbursement (C.J.)

The mean cost of the 174 inpatients was NOK71,206 (95% CI NOK47,456-94,956) according to the DRG weights while it was NOK56,653 (95% CI NOK48,278-65,028) among the controls when controlling for primary diagnosis (MC1). When controlling for hospital and ward (MC3), the mean cost of the 174 inpatients was NOK74,644 (95% CI NOK50,820-98,468) according to the DRG weights, while it was NOK49,511 (95% CI NOK44,363-54,659) among the controls. There were minimal differences (less than NOK750) in reimbursement when comparing MRSA outpatients (C3) and day patients (C4) with their respective controls (MC5 and MC6). In both analyses, the bootstrapped 95% CI were slightly wider in the cases compared with their respective controls, but there was no significant difference in either group.

6.3.2 Length of stay (C.J.)

The two analyses of LOS for inpatients both revealed that MRSA inpatients (n=174) stay in the hospital approximately 3 days longer, on average, compared with their respective controls (MC2 and MC3). The bootstrapped 95% CI showed no overlap between cases and controls, in either analysis, indicating a significant difference between the groups. The span of the 95% CI in the controls did not exceed 1.5 days; where as, the span of the 95% CI in the cases was approximately 3 days.

6.3.3 Subsequent episodes of care (C.J)

The MRSA positive inpatients (n=174) had almost twice as many subsequent episodes compared to their matched controls (MC3). There was a significant difference in this analysis revealed by the bootstrapped 95% CI (Table 3). The other analyses showed that the number of subsequent episodes of care for all MRSA patients (n=315) was slightly less than the controls (MC4). When the patients were analyzed according to the level of care, outpatient (n=241) and day patient (n=20), the MRSA cases continued to have a slightly lower number of subsequent episodes of care compared with their respective controls. Only the MRSA inpatients (n=174) had a significant difference in the number of subsequent episodes.

6.3.4 Cost of excess LOS (A.E.S.A.)

The cost of additional LOS for the MRSA inpatients (n=174) was based on the average DRG fraction including overhead costs, care costs, imaging services, and laboratory costs per additional day. This represented 87% of the total DRG cost weights, which translated to an average of NOK7,863 per additional day in hospital. MRSA inpatients had a mean excess LOS of three days compared with their matched controls. Hence, the average total additional cost of excess LOS for MRSA inpatients is estimated to be NOK23,589 per case.

Table 3: Comparison of costs, LOS, and subsequent episodes of care between MRSA patients and matched controls

Analysis	Groups of comparison	n	Results (<i>bootstrapped 95% CI</i>)	
Mean cost per episode of care based on DRG cost weights	C1 vs MC1	144 vs 527	NOK71,206 (47,456 -94,956)	NOK56,653 (48,278-65,028)
Mean length of stay (days)	C1 vs MC2	162 vs 606	8.5 (6.9 - 10.1)	5.4 (4.9 - 6.1)
Mean cost per episode of care based on DRG cost weights	C1 vs MC3	170 vs 671	NOK74,644 (50,820-98,468)	NOK49,511 (44,363-54,659)
Mean length of stay (days)	C1 vs MC3	170 vs 671	8.2 (6.6 - 9.9)	4.6 (4.1 - 5.2)
Mean number of episodes of care subsequent to the initial matched episode	C1 vs MC3	170 vs 671	1.5 (1.1 - 1.9)	0.8 (0.68 - 0.89)
Mean number of episodes of hospital care at all levels	C2 vs MC4	313 vs 1247	4.1 (3.41 - 4.78)	4.2 (3.70 - 4.80)
Mean cost based on DRG cost weights	C3 vs MC5	239 vs 953	NOK1,318 (1,106 - 1,530)	NOK1,438 (1,344 - 1,532)
Mean number of subsequent episodes	C3 vs MC5	239 vs 953	2.90 (2.39 - 3.42)	3.25 (2.82 - 3.68)
Mean cost based on DRG cost weights	C4 vs MC6	19 vs 72	NOK8,435 (5,854 - 11,015)	NOK9,182 (7,640 - 10,724)
Mean number of subsequent episodes	C4 vs MC6	19 vs 72	2.42 (-1.58 - 6.42)	4.19 (-0.13 - 8.52)

7. DISCUSSION

7.1 Main summary(C.J.)

Antibiotic resistant pathogens, such as MRSA, pose a serious risk to public health. In order to control the spread and prevent an endemic presence of MRSA within its health care facilities, Norway developed comprehensive guidelines for screening and isolating patients carrying this pathogen. Currently, the activity-based financing of somatic institutions does not incorporate the additional economic burden born by hospitals to apply these guidelines. To evaluate the costs associated with patients diagnosed with MRSA who received specialized care in the South-Eastern Norway Regional Health Authority during the year 2012, we estimated and compared the LOS, the number of subsequent episodes of care, and the DRG cost weight reimbursement for MRSA patients and a series of matched control groups. Awareness of these expenditures is critical for cost-effectiveness analysis to evaluate the impact of intervention methods and infection control programs, as well as to make informed policy decisions.

7.2 Strengths of the study (C.J.)

Strengths of this study were the reliability of our proxies for cost, as well as the quality, accuracy, and completeness of the data set utilized for analyses. The data set included the actual LOS per episode of specialized care for all patients in the health region.

These results are generalizable to Norway and Norwegian hospitals as the South Eastern Norway Regional Health Authority represents the 56% of the population, and the DRG reimbursement system is a part of the national government's hospital financing scheme.

The detailed recoding of hospitals and hospital wards to identify types of wards in each hospital to create consistent codes for identical wards across the entire health region facilitated reliable matching based on ward. This type of comparison allowed for matching patients that were similar with respect to type of acute care, but not too similar that differences were not captured when matching on DRG code or primary diagnosis.

7.3 Limitations of the study (C.J.)

A general limitation that must be considered is the nature of retrospective register-based studies. Using observational data that were collected retrospectively commonly leads to the exclusion of relevant risk factors. In turn, the observational nature of the study means that only association, not causation, can be inferred. In our case, we can only assume there is a correlation with having MRSA and lengthened hospital stay, and thus increased costs, since this association could be the result of confounding. To expand, there may be other risk factors characteristic of our patient sample that contribute to their LOS, other than their MRSA status. Patients with MRSA tend to be older and sicker than the general population. Although we have attempted to control for this by matching on various criteria, we can only infer correlation.

The use of an average gross-costing measure, such as the DRG, bears with it certain limitations, and capital costs were not included. With respect to decision-making, marginal costs should be measured, including a detailed micro-costing approach. The time restriction and availability of these data limited us to the use of average cost reimbursement based on the DRG cost weight. Also, the use of the DRG reimbursement to hospitals has recently been criticized by the Office of the Auditor General of Norway

due to inconsistencies in the DRG coding practices, leading to erroneous DRG code in 1 out of 4 hospital admissions (Office of the Auditor General of Norway, 2009). On the other hand, the actual measures required to be taken when treating MRSA patients, such as isolation, material costs (caps, gowns, gloves, etc.), disinfection costs, antibiotic use, among others, are not incorporated into the DRG code reimbursement, and thus, the DRG reimbursement could be an underestimate of the actual resource burden to the hospital.

According to Cosgrove and Carmeli (2003), it is important to understand the perspective of a study when interpreting its results, as studies that evaluate one perspective can undervalue the impact of antimicrobial resistance. A hospital perspective is a limited view of the overall effect of microbial resistance on the health care system, as much of clinical care is now provided in long-term care facilities and rehabilitation centers (Cosgrove and Carmeli, 2003). This study was conducted from a hospital's perspective and focused therefore on MRSA attributable costs to the hospital. A societal perspective which considers production loss due to morbidity and death, costs to the individual (transportation, lost leisure time, lost wages), diminished quality of life, among others, would have resulted in a more comprehensive cost estimate of the economic burden that MRSA poses to society as a whole. The cost of antibiotic use to society should also be included, as the rate at which organisms are developing antimicrobial resistance is quickly eliminating the effectiveness of certain valuable antibiotics. Additionally, a significant cost to consider is the impact of isolation on the patient. According to Gould (2006), there is an association between isolated patients and poorer standards of care, as well as patients suffering from anxiety and ostracization due to isolation.

We were limited to data from one year (January 1-December 31, 2012), which is a major limitation for several reasons. Patients with a MRSA diagnosis are generally sicker and older than the average patient, and using LOS as a proxy for resource use may artificially inflate the impact of the presence of MRSA. We were unable to control for pre-MRSA status severity of illness and LOS. A longer time period of observation including pre-MRSA severity of illness would have allowed for adjustments to be made. Additionally, a one-year period does not allow for observing the long-term effects of MRSA status for the individual patients, which are known to have extended morbidity after discharge (Gould, 2006). A short-term analysis also leads to lack of information

about the cost of mortality, which was not observed in this analysis. The valuation of mortality is difficult, but should be considered a variable of interest in a long-term evaluation of cost.

7.4 Discussion of findings (both authors)

The results of this study reveal that MRSA diagnosed inpatients have an average LOS in the hospital that was three days longer than their respective matched controls (8.5 vs. 5.4 and 8.2 vs. 4.6). These findings support our hypothesis regarding this patient population's LOS in the hospital. The underlying reasons for this difference can vary and no conclusions as to the cause can be drawn. The patients in this group may have had the same average LOS without the presence of MRSA.

Something to be considered when reflecting on these findings is the Norwegian protocol of preemptive isolation of patients who are suspected of having MRSA. According to our sources from Akershus University Hospital, the average time in preemptive isolation of patients suspected of MRSA is three days. In theory, according to the national guidelines, these patients are to be treated with the same priority as all other patients, but in practice there is a possibility that patients with an "unknown" MRSA status may have delays in receiving other diagnostic exams because of the additional precautions that must be taken. For example, an unknown MRSA patient in preemptive isolation may be placed on hold for imaging services until the MRSA status is conclusive. The waiting time for screening results may contribute to delayed care for these patients, which in turn could prolong the LOS. If delays in care for patients in preemptive isolation is what occurs in practice, policy makers must explore ways to incentivize hospitals in order to assure timely care for these patients.

The prevention and control measures for MRSA are rigorous in Norwegian hospitals, adding to the time health personnel spend on each patient who is isolated. Care is provided according to the patient's needs so each case is unique. Nevertheless, there are certain routines and practices that make it necessary for staff to have contact with the isolated patient (serving of meals three times a day, blood tests, changing of bed linens every day, among other). After each contact with an isolated MRSA patient, staff must make sure that all equipment is disinfected and waste is properly disposed before it can be moved out of the isolation room. Contaminated waste means higher costs to the hospital, as this kind of waste must be handled with particular care. This indicates that

our estimates of costs related to MRSA in hospitals, based on LOS and DRG reimbursement, may have greatly underestimated the real costs of this condition.

In 2010, Jinshuo Li conducted a detailed cost-effectiveness analysis of screening methods for MRSA patients at Ullevål Hospital, which falls under the Oslo University Hospital Trust. In this analysis, Li presented details on the micro-costs of screening and preemptive isolation of suspected MRSA patients. This included testing costs, labor costs, material costs, and the cost of disinfecting the room where patients were isolated. The total cost of these resources based on the use of a bacteriological culture test for screening was NOK17,753 (NOK based on the year 2012), per episode of screening and preemptive isolation. As many Norwegians travel abroad and come in contact with foreign health care facilities, fulfilling the criteria for MRSA screening, we believe it would be advisable for the health authorities to further investigate the number of patients who are screened for MRSA with negative test results. A cost-effectiveness evaluation of the preemptive isolation and screening should be considered, as these resources may be more effectively used for other purposes.

The MRSA diagnosed inpatients (n=174) had a mean reimbursement NOK25,133 higher than their respective controls when matched according to hospital and ward (MC3) (NOK74,644 vs. 49,511) supporting our hypothesis that this patient population had on average a higher DRG cost weight reimbursement. As discussed previously, the DRG cost weight as a proxy for cost has its limitations, but what is clear from these findings is that MRSA inpatients have a higher mean reimbursement when compared with similar patients in the same hospital ward. As the MRSA status is not incorporated into this reimbursement, and neither are the actual costs of infection control measures and isolation, this difference is most likely a severe underestimate of the actual resources used by the hospital to care for these patients.

There was also a significant difference in the mean number of subsequent episodes of care when comparing inpatients (n=174) with controls matched according to ward (MC3) (1.5 vs. 0.8 episodes). The mean numbers of subsequent episodes of care were not significantly different between MRSA cases and controls when comparing all MRSA patients (n=315), outpatients (n=241), and day patients (n=20) with their respective controls (Table 3). In fact, with each comparison, MRSA patients had slightly lower average numbers of subsequent episodes. This was not expected as we hypothesized more subsequent episodes of care for MRSA patients. Again, considering

the additional resources used by hospitals to care for these patients, policy makers should enact their role as complementary agent and create incentives for timely and appropriate care. Otherwise, there could be a possibility that hospitals may try to avoid this patient population because of the extensive resources used for infection control and isolation.

7.5 Findings in other studies (A.E.S.A.)

Our results of costs per identified MRSA case in Norwegian hospitals (NOK71,206 when controlling for primary diagnosis and NOK74,644 when controlling for hospital and ward) are in accordance with previous studies such as the German study by Hübner et al. (2014) in which the cost per identified MRSA case was estimated to €8,673, which with an average exchange rate of NOK7,48 for 2012, is equivalent to NOK64,874. One important distinction from the German study is that we have used a gross-costing measure, the DRG, to estimate the costs related to MRSA, while the German authors have accounted for costs related to hygienic measures, laboratory and opportunity costs of blocked beds. Opportunity cost of blocked beds accounted for 77% of the total cost per case of MRSA in the German study. This is likely a significant cost for Norwegian hospitals also as there are issues with having enough capacity for inpatient stays. Although, being that individual Norwegian hospitals are structured differently and have capacity issues of varying degrees, estimating the opportunity cost of bed blocking is difficult, but should be considered in future studies. Excess LOS as estimated by Hübner et al. was 2.6 days for MRSA patients when compared to other patients in the same G-DRG classification, which is very close to our findings of average excess LOS of 3 days for MRSA patients when compared to their control groups.

Another study, performed by Swiss authors Macedo-Viñas et al. in 2013 at the University of Geneva Hospitals, estimated that additional MRSA related costs averaged CHF800 per day, which with an average exchange rate of NOK6.21 for 2012, is equivalent to NOK4,968 per day. Given our findings on mean excess LOS of at least 3 days for MRSA patients, and additional costs of NOK23,589 compared with their control groups, we have an average daily cost of NOK7,863. The Swiss authors' findings on mean excess LOS (15.3 days according matched analysis) was very different from ours (3 days). This may be explained by the fact that the Swiss study only included patients who required systemic antibiotics and had severe infections, while we included all inpatients

with a known MRSA diagnosis, regardless of severity of illness. For these reasons, the excess LOS as found in the Swiss study could possibly be explained primarily by the severity of the infections, whereas there are very few serious MRSA infections in Norway, less than 25 cases per year from year 2000 to 2010, according to the Norwegian Institute of Public Health.

An American study by Bruce Y. Lee et al. (2013) estimated the economic burden of CA-MRSA to third-party payers to \$2,277 - \$3,200 (equivalent to NOK13,252 - 18,624 with 2012 exchange rate of NOK5.82), including only direct medical costs such as outpatient/Emergency Room visit, hospitalization and treatment. Their estimated costs to society were 3-5 times higher than the third-party costs. This could possibly imply that our cost estimates based on LOS from a hospital perspective are grossly underestimating the costs MRSA poses to society, as we are not taking into consideration the cost burden imposed to society through lost productivity, lost income, lost quality of life and life years, among others.

7.6 Policy implications (both authors)

Given that the prevalence of MRSA is very low in Norway, the “search and destroy” approach seems to have positive effects and should, if possible, be carried on. According to van Rijen and Kluytmans (2009), and their analysis of a Dutch hospital, applying the “search and destroy” approach in countries with low endemic MRSA incidence saves lives and costs. The “search and destroy” method includes early detection, early identification and efforts to contain spread. Various strategies are used in this method, such as, isolation of patients, work restrictions for staff members that are colonized, screening of staff and patients, and use of decolonization methods (Hughes et al., 2013).

The implementation and adherence to the national guidelines (MRSA-Veilederen) for preventing and containing the spread of MRSA in Norwegian health care facilities should be continuously followed up in the most populated health regions. However, the most costly and transcendent control measure, contact isolation in single room, has been associated with reduced contact between health care workers and the patient by 40%-50%, reduced quality of patient care and adverse psychological impact on the patient (Wassenberg, 2010). These guidelines should, therefore, be under constant supervision from policymakers, and continuously revised according to the ever-changing health

threat situation, in consensus with professionals in the area. It should be a goal to reduce the number of days patients spend in isolation if their MRSA diagnosis result is negative.

With increased patient mobility in Europe and particularly, within the EU, there is also a risk of patients who receive care abroad, getting infected with bacteria and viruses which the Norwegian health care system has managed to keep under control. Hence, it is important that screening practices continue, are refined, and that policy makers prioritize sustained development of screening methods.

The economic burden of MRSA in hospitals is high, primarily due to the increased LOS and the extensive hygienic measures that must be taken to contain the spread of MRSA (Hübner et al., 2014). As of today, hospitals in Norway do not have a practice of accounting for the additional cost burden of MRSA and are not being fully reimbursed for these costs. Therefore, there is a need for more information about the detailed costs associated with MRSA. Quantifying the additional LOS for MRSA inpatients is important for the fiscal stability of hospitals and the overall health care budget.

The importance of incentivizing infection controls measure in hospitals cannot be overstated, especially when considering the unseen cost savings of preventing the spread of antimicrobial resistance. As discussed in chapter 3.3, it is the policy maker's role to act as a complimentary agent so that they can bring balance to the principal-agent relationship. For policy makers to act in the best interest of MRSA patients, as well as the overall population, they must be adequately informed of the resources used and economic burden of this group. A lack of information about the costs of MRSA raises concerns with regards to the spread of the infection within hospital settings and health care facilities, as well as, increased antibiotic resistance in the population due to overuse and non-adherence to treatment. We advise that policy makers consider a national methodology for somatic institutions to systematically account for the detailed costs of the extensive hygienic measures, the cost of isolation, and the additional labor costs associated with caring for MRSA patients. With an accurate account of the economic burden of MRSA in hospitals, correct remuneration could be assured to incentivize quality care for this patient population, and in turn, contain the spread of antimicrobial resistance in Norway.

8. Conclusion (both authors)

To our best knowledge, this is the first study to estimate the cost burden of MRSA in hospitals in the South-Eastern Norway Regional Health Authority. A statistically significant difference in LOS was seen between MRSA inpatients (n=174) and respective matched controls (MC2 and MC3). MRSA patients were also more costly than respective controls, based on their DRG reimbursement. In addition, there was a significant difference in the number of subsequent episodes of care for MRSA inpatients (n=174) compared with matched controls (MC3). These measures of resource use are most likely an underestimate of the economic burden of this patient population.

This study may be used as starting point for future economic evaluations to further assess the extent of the economic and societal impact of MRSA. It is essential that additional study in this area be done to estimate the micro-costs of infection control measures, the cost of isolation, and the marginal costs of caring for this patient population. Additional research should consist of various perspectives, including but not limited to, the hospital perspective. The health authorities should consider and further explore the potential imbalance in the hospital reimbursement for this patient population so that hospitals may be appropriately incentivized to provide proper and timely care. The extensive infection control measures applied in Norwegian health care facilities are resource intensive. Further study and economic evaluations are imperative so that policy makers may be sufficiently informed when priority setting and decision-making is involved.

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Appendices

Appendix A

List of relevant variables

Table 4: Relevant variables from MSIS and NPR

Variable Name	Explanation
Main Groups	
MRSA status	1: MRSA-positive 0: MRSA-negative
Positive	1: MRSA-positive & registered in NPR
Negative	1: MRSA-negative & registered in NPR
Database	1: NPR-data 0: MSIS-data
Episode	Episode = Episode-serial number. Each patient has received a serial number for each new episode in the hospital (the first treatment in the hospital is designated xhlnr=1) Each patient that is only registered in MSIS also has the designation xhlnr=1
Descriptive variables from both MSIS and NPR	
Sex	1: Male 0: Female
Municipality	Municipality of residence
District	District patient resides in
Descriptive variables only from MSIS data	
Ethnicity	Ethnicity based on mother and father's place of birth (ancestry) 1: Norwegian (born in Norway, Norwegian born parents) 2: second generation immigrants (born in Norway, foreign born parents or adopted from abroad) 3: first generation immigrants (born abroad, reside in Norway) 4: Temporary stay (born and live abroad) 9: unknown (not registered)
Norwegian birth	1: born in Norway 0: born abroad
County	County that patient lives in and is registered
Diagnosis	1: MRSA-infection 0: MRSA-carriage
MRSA type	Genotype (<i>spa</i> -type) for bacterial isolates
PVL	PVL = Panton Valentin Leukocidin: a gene associated with increased virulence 1: PVL-positive 2: PVL-negative
VRE	VRE = infection/ carrier of Vancomycin-resistant Enterococci 1: VRE-positive 0: VRE-negative

Descriptive variables only from NPR data	
Age	Age: numeric integers, range 0 – 113
Age group	Age group: numeric, 10-year intervals
Episodes total	Total episodes per patient
Description of episodes only in NPR data	
Outpatient	1: outpatient consultation 0: other episode in hospital (day or inpatient treatment)
Day treatment	1: day treatment 0: other episode in hospital (outpatient clinic consultation or day treatment)
Admitted	1: admitted as inpatient 0: other episode in hospital (outpatient consult or day treatment)
Screening date	Date for MRSA screening test
In date	Date for hospital treatment (outpatient clinic, day treatment, inpatient admission)
Out date	Date of release
Days	Total days of treatment (in date minus out date) Outpatient clinic and day treatment are assigned 1 instead of 0
Screening days	Number of days from MRSA test to hospital treatment (+ n: positive MRSA test was taken before or the day of treatment, -n: positive MRSA sample was taken after treatment)
Known MRSA	1: MRSA diagnosis assigned before or the day of treatment 0: MRSA diagnosis was assigned after the start of treatment
Hospital diagnosis	1: MRSA diagnosed started treatment in hospital 0: MRSA was diagnosed in healthcare facility other than hospital
Health code	Numeric code for health: 11 – 25
Hospital code	Numeric code for hospital - physical location, 11 - 55
Department	Code (string) for each department, based on variable department names (code numbers.) ward type and hospital
Department code	Numeric code for department
Corrected department codes	Numeric code for department after correcting coding errors

Appendix B

Groups of analysis

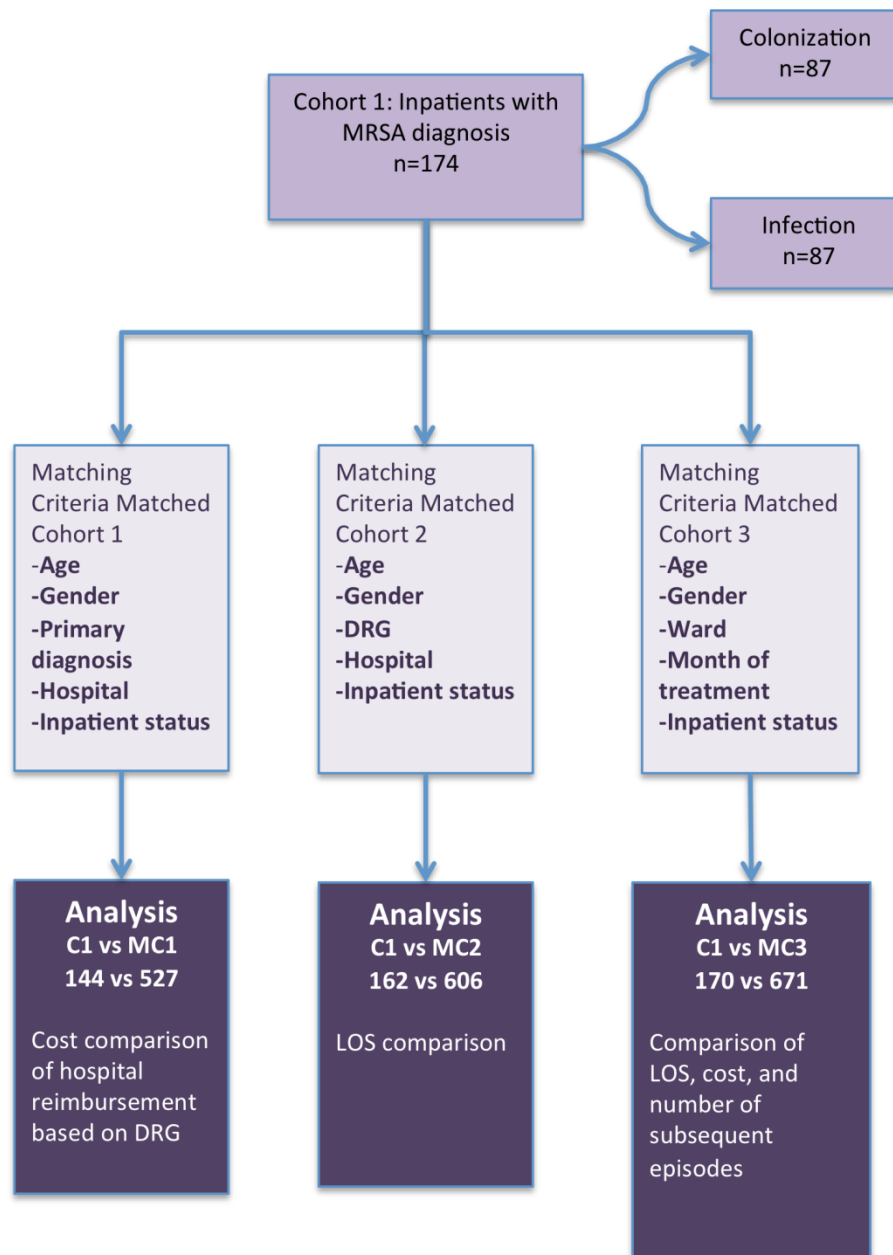


Figure 19: Flow chart of inpatient analysis (n=174)

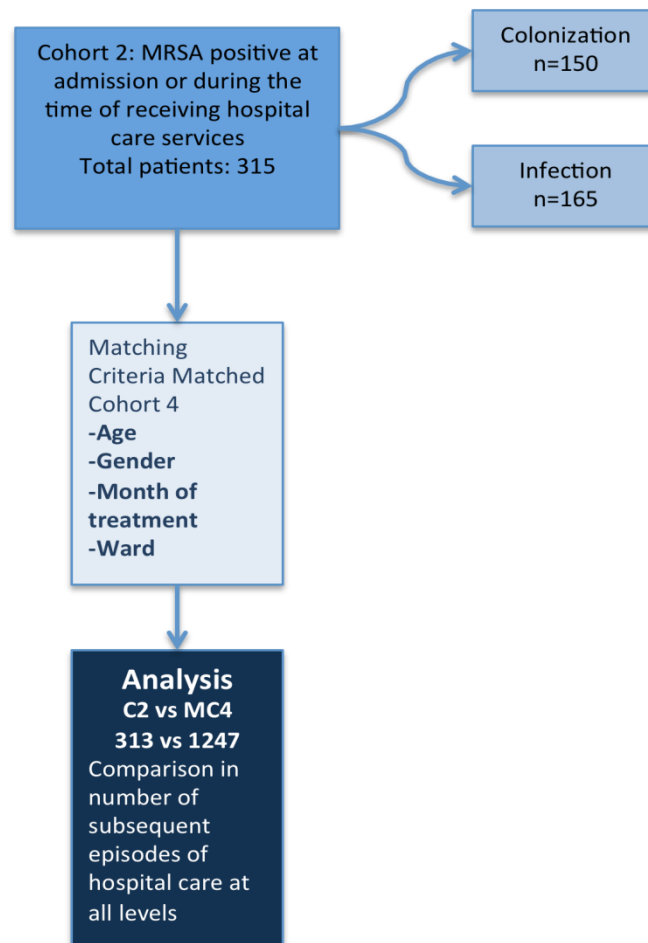


Figure 20: Flow chart of analysis of all MRSA patients (n=315)

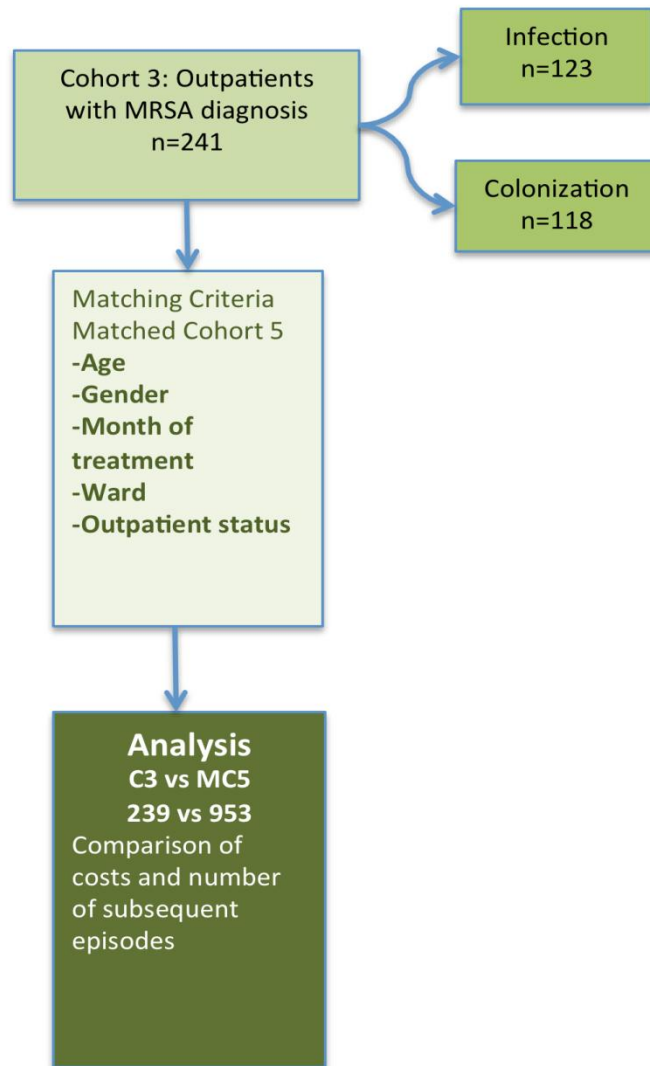


Figure 21: Flow chart of outpatient analysis (n=241)

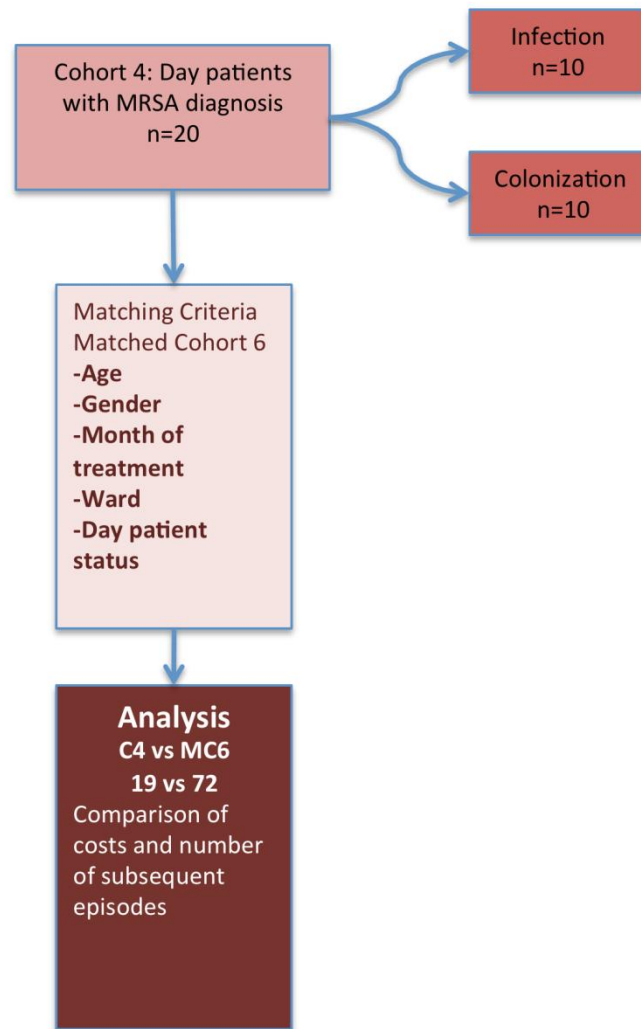


Figure 22: Flow chart of day patient analysis (n=20)

Appendix C

Primary diagnoses of MRSA patients

Table 5: The most common illnesses among MRSA positive patients (n=315)

Primary diagnosis code	Description	Frequency (%) of total	
L02	Cutaneous abscess, furuncle and carbuncle	28	8,86 %
Z03	Encounter for medical observation for suspected diseases and conditions ruled out	7	2,22 %
Z01	Routine examination of specific system	6	1,90 %
Z09	Encounter for follow-up examination after completed treatment for conditions other than malignant neoplasm	6	1,90 %
Z36	Encounter for antenatal screening of mother	6	1,90 %
K61	Abscess of anal and rectal regions	5	1,58 %
A41	Sepsis due to <i>Staphylococcus aureus</i> or MRSA	5	1,58 %
A46	Erysipelas: An acute infection of the skin caused by species of streptococcus.	5	1,58 %
J44	Other chronic obstructive pulmonary disease	4	1,27 %
L08	Other local infections of skin and subcutaneous tissue	4	1,27 %
N61	Inflammatory disorders of breast	4	1,27 %
S01	Open wound of head	4	1,27 %
S06	Intracranial injury. Brain injury resulting from an accident, surgery, or other trauma.	4	1,27 %
Z22	Carrier of infectious disease	4	1,27 %
Z37	Outcome of delivery	4	1,27 %

(icd10data.com, 2015)

Table 6: The most common illnesses among inpatients (n=174)

Primary diagnosis code	Description	Frequency (%) of total	
Z37	Outcome of delivery	15	8,62 %
L02	Cutaneous abscess, furuncle and carbuncle	13	7,47 %
A41	Sepsis due to <i>Staphylococcus aureus</i> or MRSA	6	3,45 %
A46	Erysipelas: An acute infection of the skin caused by species of streptococcus.	4	2,30 %
K61	Abscess of anal and rectal regions	4	2,30 %
S06	Intracranial injury. Brain injury resulting from an accident, surgery, or other trauma.	4	2,30 %
T81	Complications of procedures	4	2,30 %
I63	Cerebral infarction: An ischemic condition of the brain, producing a persistent focal neurological deficit in the area of distribution of the cerebral arteries.	3	1,72 %
J15	Bacterial pneumonia. Bronchopneumonia due to bacteria other than <i>S. pneumoniae</i> and <i>H. influenzae</i>	3	1,72 %
J44	Other chronic obstructive pulmonary disease	3	1,72 %
J45	Asthma: A chronic respiratory disease manifested as difficulty breathing due to the narrowing of bronchial passageways.	3	1,72 %
L08	Other local infections of skin and subcutaneous tissue	3	1,72 %
N17	Acute kidney failure	3	1,72 %
Q37	Cleft palate with cleft lip. Cleft lip and cleft palate are birth defects that affect the upper lip and roof of the mouth	3	1,72 %
R07	Pain in throat and chest	3	1,72 %

(icd10data.com, 2015)

Appendix D

Structural organization of the South-Eastern Norway Regional Health Authority

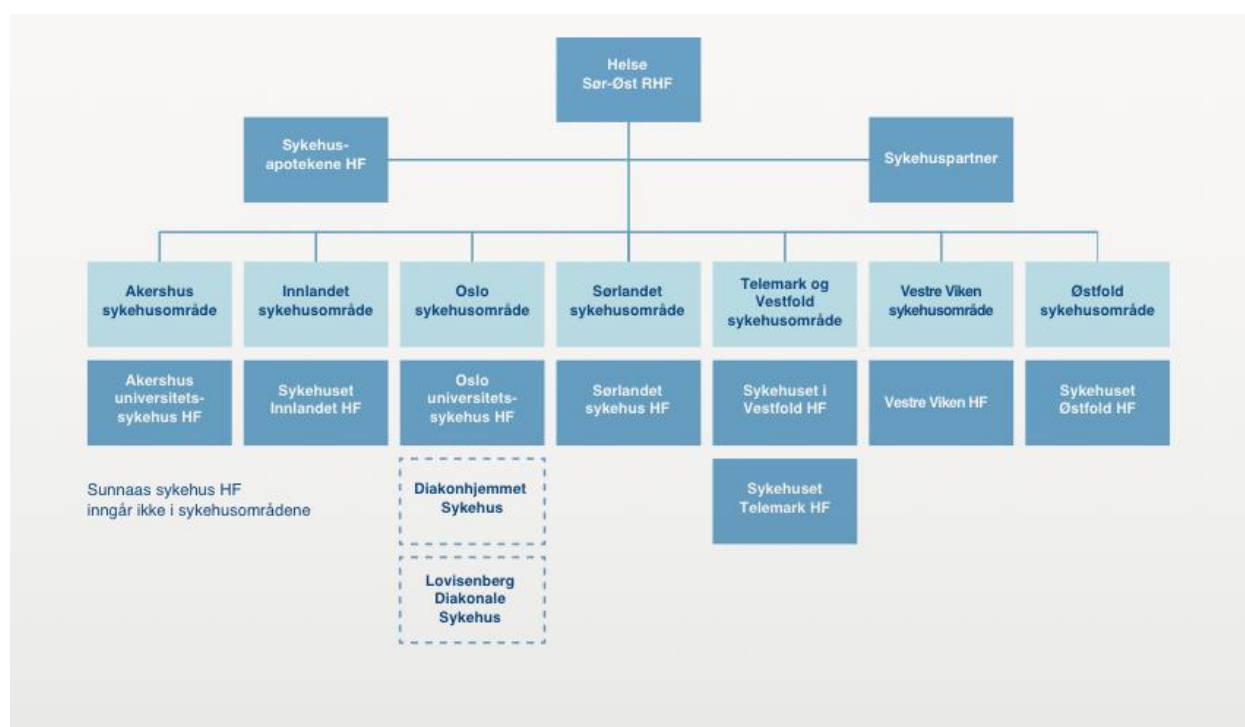


Figure 23: Structural organization of the South-Eastern Norway Regional Health Authority
(Helse Sør-Øst, 2012)

Appendix E

MRSA cases in Norway from 2006-2013

Table 7. Infection and colonization with Methicillin-resistant *S. aureus* (MRSA) in Norway 2006-2013 according to year of diagnosis and place of contraction

Year	2006	2007	2008	2009	2010	2011	2012	2013
Health care facility in Norway	253	216	202	205	232	228	236	291
Community	218	218	230	318	332	406	457	558
Abroad	159	170	226	296	345	425	515	633
Total	630	604	658	819	909	1059	1208	1482

(Norwegian Institute of Public Health, 2015)

Appendix F

Methicillin-resistant *Staphylococcus aureus* in Europe from 2012

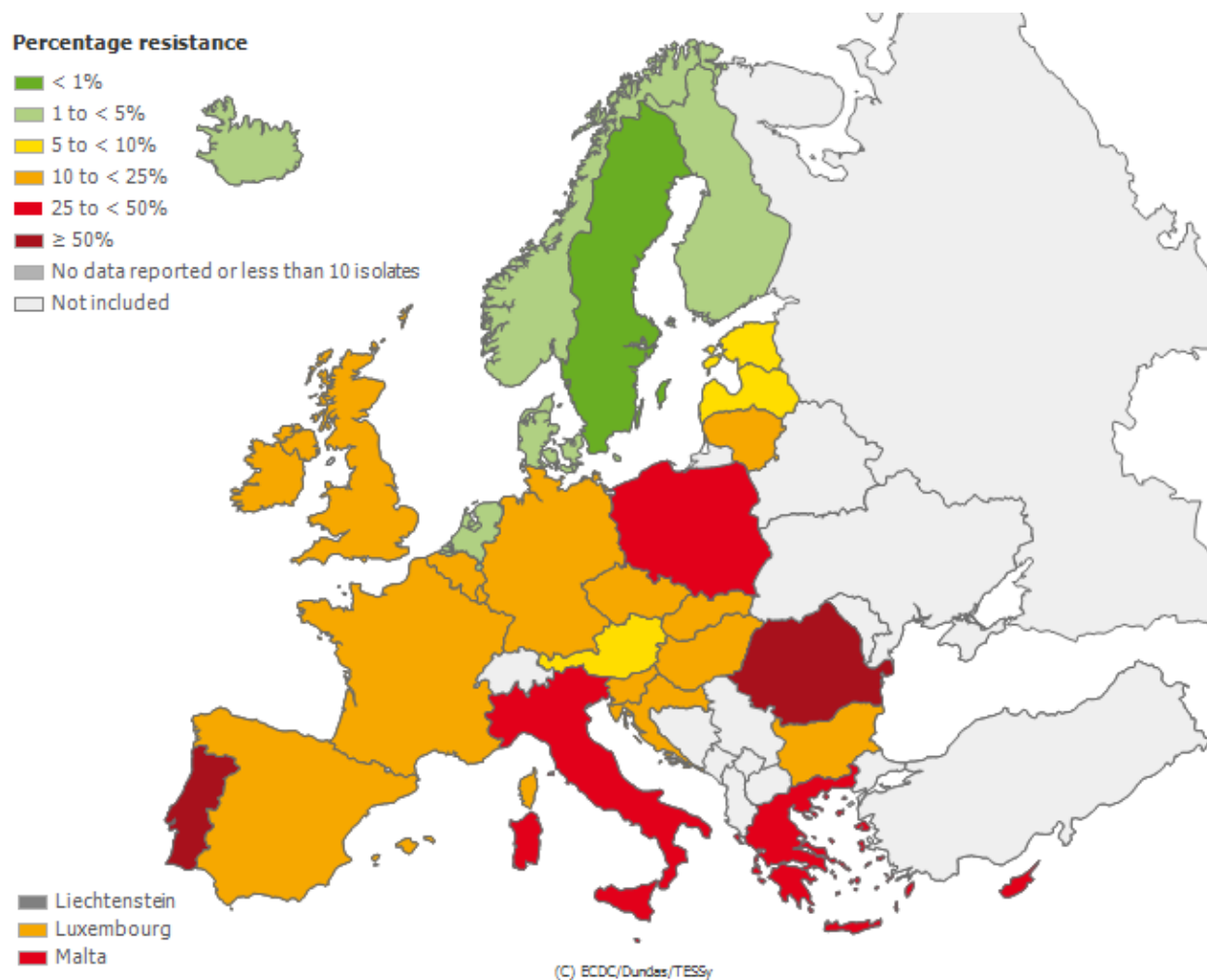


Figure 24: Proportion of Methicillin Resistant *Staphylococcus aureus* (MRSA) Isolates in Participating Countries in 2012

(ECDC, 2012)

Appendix G

Contact isolation protocol and screening criteria

Table 7: Description of protocol for contact isolation

KONTAKTSMITTEISOLERING MED MUNNBIND (KI m/munnbind) Døren inn til pasientrommet må holdes lukket.	
Smittefrakk	Brukes ved direkte kontakt med pasienten eller forurensset utstyr. Ved fare for søl, beskytt smittefrakken med plastforkle. I forgang henges frakken med innsiden ut. Inne i pasientrommet henges frakken med utsiden ut. Skiftes etter hovedstell og ved evt. tilsøining.
Hansker	Skal brukes ved all kontakt med pasienten og ved all kontakt med seng og mulig infisert utstyr, gjenstander eller flater.
Munnbind, briller/visir, lue/hette	Bruk munnbind (visir) når du går inn i rommet. Ved enkelte av de sykdommer som smitter via store dråper, behøver man bare bruke munnbind når du arbeider i nærkontakt med pasienten (< 1m fra pasienten). Se sykdomsliste for hvilke mikrober dette gjelder.
Håndhygiene	Håndhygiene skal alltid utføres når hendene er blitt forurensset under arbeid inne i pasientrommet, og alltid før rommet forlates.
Bestikk/servise	Vanlig bestikk og servise benyttes. Dobbeltemballeres og varmedesinfiseres i seksjonens dekontaminator/ instrumentvaskemaskin. Serveringsbrettet brukes kun til transport av mat og drikke, og skal ikke settes på nattbordet o.l inne i isolatet.
Flergangsutstyr (stetoskop, lommelykt, vaskevannsfat osv.)	Oppbevares inne i pasientrommet. Dobbeltemballeres og varmedesinfiseres i seksjonens dekontaminator/ instrumentvaskemaskin.
Laboratorieprøver	Staseslange og holder til blodprøvetaking oppbevares i pasientrommet. Rekvisisjoner og prøver merkes med gjeldene smitteregime. Prøveglassene transporteres til laboratoriet i henhold til lokale retningslinjer.
Skittentøy/tekstiler	Legges i gul plastpose inne i pasientrommet, som lukkes med strips og dobbeltemballeres i tøysekk før det tas med ut på desinfeksjonsrommet.
Smitteavfall	Legges i gul plastpose i pasientrommet. Posen lukkes forsvarlig før den dobbeltemballeres i gul avfallssekk på desinfeksjonsrommet. Stikkende og skjærende avfall skal direkte i kanyleboks som henger på veggen i pasientrommet.
Transport av pasient ut av rommet	Bør unngås. Dersom det er nødvendig skal tøy, bandasjer, evt. bleie være nyskiftet, pasienten skal utføre håndhygiene før rommet forlates og benytte kirurgisk munnbind. Hvis pasienten må transporteres i seng, skal denne være ren.
Rengjøring	Rengjøringspersonalet skal alltid bruke smittefrakk og hansker ved rengjøring av pasientrommet. Rengjøring skjer på lik linje med andre pasientrom. Rombundet rengjøringsutstyr, som desinfiseres ved opphør av isolasjon.
Flekkdesinfeksjon	Ved søl av infisiøst materiale skal det alltid utføres flekkdesinfeksjon.
Besøkende	Må instrueres i smitteforhåndsregler og bruk av beskyttelsesutstyr.
Opphør av isolasjon	Se "opphør av isolasjon" i PPS.

(Ahus, 2015)

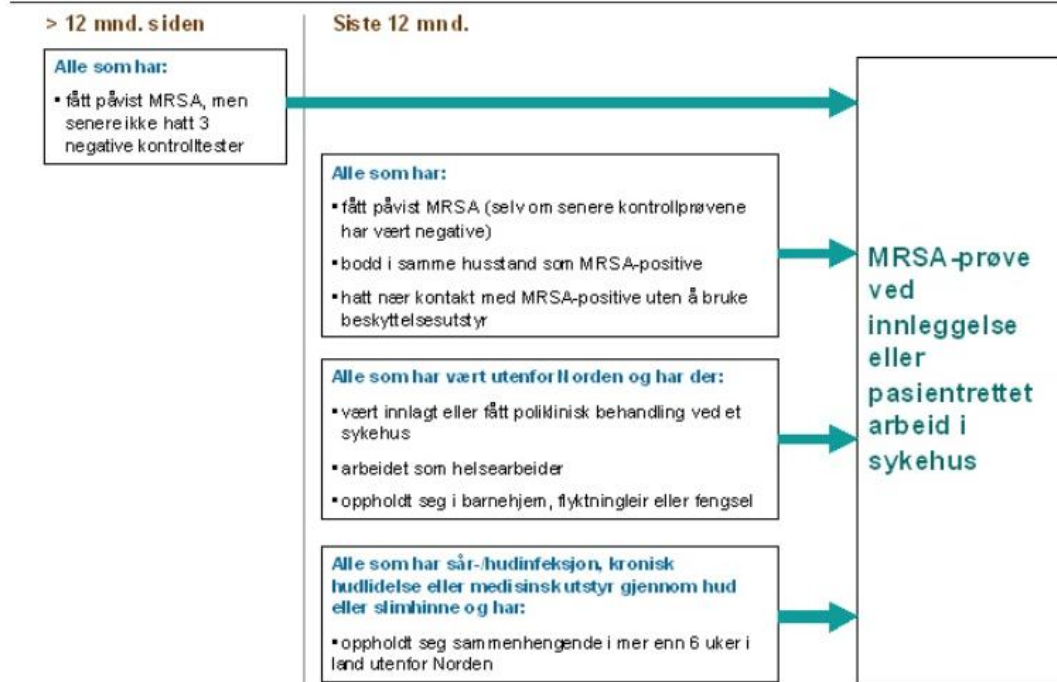


Figure 25: Screening criteria for MRSA test

(Ahus, 2015)